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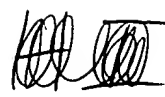
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# EUROPEAN PATENT APPLICATION

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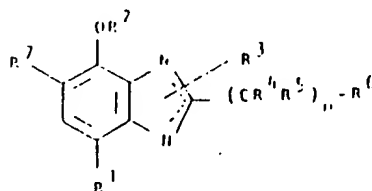
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(54) Novel compounds.

(57) Compounds of the general formula I



$R^1$  represents hydrogen, halogen or lower alkyl,  
 $R^2$  represents a lower alkyl or a substituted or unsubstituted carbocyclic aryl group,  
 $R^3$  represents hydrogen or a lower alkyl, and  
 $n$  is 0 to 8,  $n$  being 0 when  $R^3$  represents lower alkyl.  
 are disclosed as an active therapeutic substances for the treatment of inflammatory conditions, allergic conditions and disorders related to loss of gastro-intestinal integrity

or pharmaceutically acceptable salts or solvates thereof, in which

$R^1$  represents hydrogen or a lower alkyl group.

$R^2$  represents hydrogen, a lower alkyl group, or

$R^3$  represents hydrogen, a lower alkyl group, or

$R^4$  represents hydrogen or a lower alkyl group.

$R^5$  represents hydrogen or a lower alkyl group.

$R^6$  represents hydrogen, a lower alkyl, a substituted or unsubstituted aryl group, or  $-COOR^6$ .

NOVEL COMPOUNDS

The present invention relates to benzimidazoles, processes for their manufacture, pharmaceutical preparations containing them, and their use in the treatment of various disorders.

It is known that certain arachidonic acid metabolites may produce harmful effects in man. For example, products produced via lipooxygenation of the acid, for example the leukotrienes, are implicated in the pathology of arthritis and inflammation, as well as in the production and the pathology of asthma and other allergic diseases. Accordingly, a compound capable of selectively inhibiting 5-lipoxygenase while having weaker inhibiting effects on the cyclo-oxygenase enzyme is beneficial by preventing the formation of inflammatory and bronchoconstrictor mediators while having little inhibitory effect on protective prostaglandins in the stomach or on the bronchodilatory cyclo-oxygenase products, for example, prostacyclin.

Further, products of the lipoxygenase pathway may adversely affect the integrity of the gastro-intestinal mucosa. Inhibition of lipoxygenase activity may lead to stimulation of cytoprotective prostaglandin production, particularly prostacyclin and PGE<sub>2</sub>. This inhibition may therefore be of use in maintaining or establishing the integrity of the gastro-intestinal mucosa.

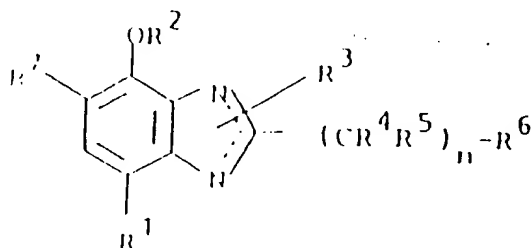
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We have now found that certain benzimidazoles inhibit the 5-lipoxygenase enzyme, and accordingly the present invention provides a benzimidazole containing an optionally etherified or esterified hydroxy group in the 4-position and a lipophilic group, the latter advantageously being in the 2-position.

The compounds of the invention find use in the treatment of inflammatory conditions, for example rheumatism and arthritis, in the treatment and prophylaxis of bronchial asthma, rhinitis, hay fever and allergic eczema, and in the treatment of disorders related to loss of gastro-intestinal integrity, for example peptic ulcers, mucosal erosions and erosive gastritis.

U.S. Patent No. 2663712, DE-OS 1921911 and J.C.S., [1956] 569 disclose certain benzimidazoles; there is, however, in none of these documents any suggestion of the possibility that any of the compounds disclosed may have any pharmaceutical use. Certain of these compounds were disclosed in J. Pharm. and Pharmacol 1956, 8, 661-5 and reported to have no significant antibacterial activity.

More especially, the present invention provides a compound of the general formula I



or a salt or solvate, e.g., hydrate, thereof, in which,  
 $R^1$  represents hydrogen or a lower alkyl group,

$R_2$  represents hydrogen, a lower alkyl group, or  $\overset{O}{\parallel}CR^8$ ,

$R^3$  represents hydrogen, a lower alkyl group, or  $\overset{O}{\parallel}CR^8$ ,

$R^4$  represents hydrogen or a lower alkyl group,

$R^5$  represents hydrogen or a lower alkyl group,

$R^6$  represents hydrogen, a lower alkyl, a substituted or unsubstituted aryl group, or  $-COOR^{15}$ ,

$R^7$  represents hydrogen, halogen or lower alkyl,

$R^8$  represents a lower alkyl or a substituted or unsubstituted carbocyclic aryl group,

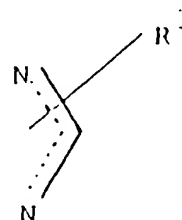
$R^{15}$  represents hydrogen or a lower alkyl,

and  $n$  is 0 to 8,  $n$  being 0 when  $R^6$  represents lower alkyl,

as an active therapeutic substance.

When used herein with reference to alkyl or alkoxy groups, the term "lower" means that the group contains up to 6 carbon atoms, preferably up to 4 carbon atoms. Alkyl radicals may have straight or branched chains, and may be, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl or *tert*-butyl.

In formula I, the symbol



means that  $R^3$  may be attached to either of the nitrogen atoms of the imidazole ring and that, when  $R^3$  represents hydrogen, tautomerism exists; both tautomers are included within the scope of this invention. When  $R^3$  does not represent hydrogen, the two compounds

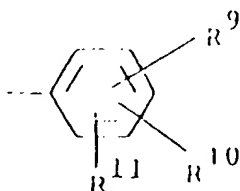
differ because of the asymmetry of the benzene ring substituents, and both compounds are included within the scope of this invention.

When  $R^1$  represents a lower alkyl group, it is advantageously a methyl. It is preferred that both  $R^2$  and  $R^3$  represent hydrogen; when either of them represents lower alkyl, it is advantageously the methyl group and when either of

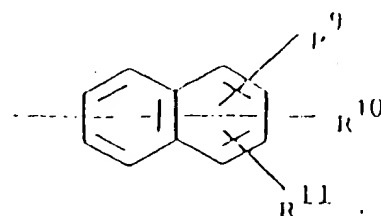
them represents  $\overset{\text{O}}{\parallel}\text{CR}^8$  it is advantageous that  $R^8$  represents methyl. It is preferred that both  $R^4$  and  $R^5$  represent hydrogen; when either of them represents lower alkyl, methyl is advantageous.

When  $R^4$  and  $R^5$  are different, stereoisomerism may arise and it will be appreciated that the present invention provides all isomers individually and in admixture.

When  $R^6$  or  $R^8$  represents aryl, the group may be carbocyclic group, suitably



, which is preferred, or

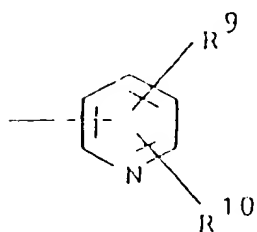
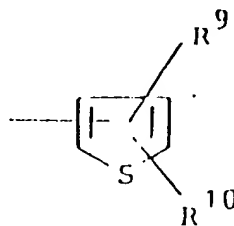


in which each  $R^9$ ,  $R^{10}$ ,  $R^{11}$  independently represents hydrogen, hydroxy, lower alkoxy, e.g., methoxy, lower alkyl, e.g., methyl, or halogen, preferably chlorine or bromine, trifluoromethyl, nitrile, nitro, amino,  $NR^{12}$ ,  $R^{13}$  (in which  $R^{12}$  and  $R^{13}$  are independently hydrogen or lower alkyl),  $-COOH$ ,  $-COOR^{14}$ ,

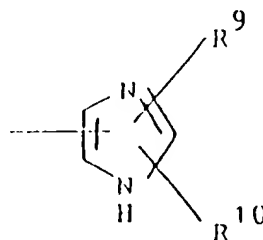
$\begin{array}{c} O \\ || \\ -C-R^{14} \end{array}$ , or  $\begin{array}{c} O \\ || \\ -O-C-R^{14} \end{array}$  (in which  $R^{14}$  is lower alkyl or aryl), or in which  $R^9$  and  $R^{10}$  are linked and together represent methylenedioxy or  $C_3-C_4$  alkylene.

In the case of a substituted naphthyl group the substituent, or each substituent independently if there are more than one, may be on either the linked ring or the non-linked ring.

Alternatively  $R^6$  may represent a heterocyclic aryl group, suitably



or



in which  $R^9$  and  $R^{10}$  have the meanings given above.

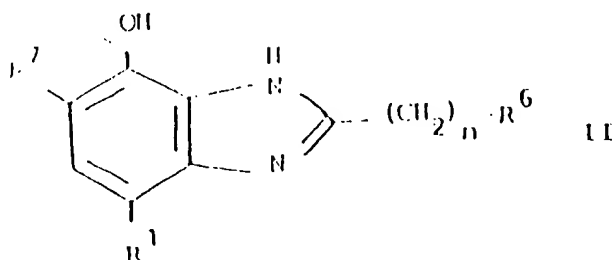
When  $R^6$  represents imidazolyl or pyridyl, it advantageously represents 1-imidazolyl or 3- or 4-pyridyl.

When  $R^6$  represents  $COOR^{15}$ , then advantageously  $R^4$  and  $R^5$  represent hydrogen.

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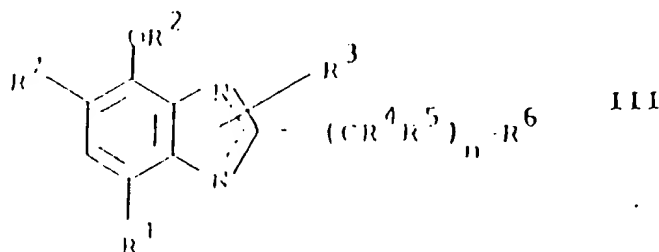
When  $R^7$  represents a halogen, chlorine is preferred; when it represents an alkyl group, tert-butyl is preferred.

Within the compounds of formula I are a preferred group of compounds of formula II



in which  $R^1$  represents a lower alkyl, particularly methyl, group,  $R^7$  represents hydrogen or a lower alkyl, particularly tert-butyl, group,  $R^6$  represents an aryl group, particularly phenyl, mono, di or tri-substituted with methoxy or methyl, and  $n$  is 0 to 5, particularly 1.

The present invention further provides a compound of the general formula III



or a salt or solvate thereof, in which  $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$  and  $R^{15}$  are as defined for formula I, subject to the provisos that in a compound in which  $R^2$  and  $R^3$  represent hydrogen or lower alkyl,  $R^6$  represents hydrogen, lower alkyl or carbocyclic



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01  
02 aryl, R<sup>7</sup> represents H or alkyl and n = 0, R<sup>1</sup> does not  
03 represent hydrogen, and that in a compound in which R<sup>1</sup>,  
04 R<sup>2</sup>, R<sup>6</sup> and R<sup>7</sup> represent hydrogen or methyl and n = 0,  
05 R<sup>3</sup> does not represent hydrogen or an alkyl group having  
06 up to 4 carbon atoms.

07  
08 Preferred substituents within the above-mentioned  
09 substituents are as indicated with reference to formula  
10 I and formula II. It will be appreciated that when R<sup>3</sup>  
11 represents hydrogen tautomerism exists corresponding to  
12 that existing in Formula I.

13  
14 The present invention also provides a physiologically  
15 tolerable compound of the general formula I, or a  
16 physiologically tolerable salt or solvate thereof, for  
17 use in treatment of the human or animal body.

18  
19 The present invention also provides a pharmaceutical  
20 preparation comprising a physiologically tolerable  
21 compound of the general formula I, or a physiologically  
22 tolerable salt or solvate thereof, in admixture or  
23 conjunction with a pharmaceutically acceptable carrier.

24  
25 Preferably, a pharmaceutical preparation of the  
26 invention is in unit dosage form and in a form adapted  
27 for use in the medical or veterinarial fields. For  
28 example, such preparations may be in a pack form  
29 accompanied by written or printed instructions for use  
30 as an agent in the treatment or prophylaxis of any of  
31 the disorders mentioned above.

32  
33 The suitable dosage range for the compounds of the  
34 invention may vary from compound to compound and may  
35 depend on the condition to be treated. It will also  
36 depend, inter alia, upon the relation of potency to  
37 absorbability and the mode of administration chosen.

01 The compound or preparation of the invention may be  
02 formulated for administration by any route, the  
03 preferred route depending upon the disorder for which  
04 treatment is required, and is preferably in unit dosage  
05 form or in a form that a human patient may administer  
06 to himself in a single dosage. Advantageously, the  
07 preparation is suitable for oral, rectal, topical,  
08 parenteral-intravenous or intramuscular administration  
09 or through the respiratory tract. Preparations may be  
10 designed to give slow release of the active ingredient.  
11

12 Preparations may, for example, be in the form of  
13 tablets, capsules, sachets, vials, powders, granules,  
14 lozenges, reconstitutable powders, or liquid  
15 preparations, for example solutions or suspensions, or  
16 suppositories. Preparations which are especially  
17 suitable for administration to the respiratory tract  
18 and for topical administration are discussed in more  
19 detail below.  
20

21 The preparations, for example those suitable for oral  
22 administration, may contain conventional excipients  
23 such as binding agents, for example syrup, acacia,  
24 gelatin, sorbitol, tragacanth, or  
25 polyvinylpyrrolidone; fillers, for example lactose,  
26 sugar, maize-starch, calcium phosphate, sorbitol or  
27 glycine; tabletting lubricants, for example magnesium  
28 stearate; disintegrants, for example starch,  
29 polyvinylpyrrolidone, sodium starch glycolate or  
30 microcrystalline cellulose; or pharmaceutically  
31 acceptable setting agents such as sodium lauryl  
32 sulphate.  
33  
34

01  
02 solutions: the compound may be dissolved in water for  
03 injection and filter sterilized before filling into a  
04 suitable vial or ampoule and sealing. Advantageously,  
05 adjuvants, for example a local anaesthetic, a  
06 preservative and buffering agents can be dissolved in  
07 the vehicle. To enhance the stability, the  
08 compositions can be frozen after filling into the vial  
09 and the water removed under vacuum. Parenteral  
10 suspensions are prepared in substantially the same  
11 manner, except that the compound is suspended in the  
12 vehicle instead of being dissolved, and sterilization  
13 is not accomplished by filtration. The compound may be  
14 sterilized by exposure to ethylene oxide before  
15 suspending in the sterile vehicle. Advantageously, a  
16 surfactant or wetting agent is included in the  
17 composition to facilitate uniform distribution of the  
18 compound.

19  
20 Preparations especially suitable for administration to  
21 the respiratory tract include, for example, a snuff, an  
22 aerosol, a solution for a nebulizer, or a microfine  
23 powder for insufflation, alone or in combination with  
24 an inert carrier such as lactose. In such a case the  
25 particles of active compound suitably have diameters of  
26 less than 50 microns, preferably less than 10 microns.

27  
28 For topical administration, the preparations may also  
29 be presented as an ointment, cream, lotion, gel,  
30 aerosol, or skin paint for topical application.

31  
32 For use in the treatment or prophylaxis of allergic  
33 disorders, in any of the preceding formulations, a  
34 suitable dosage unit may contain 0.01 to 500 mg of  
35 active ingredient, more suitably 1 to 500 mg for use  
36 via the oral route, 0.01 to 10 mg via inhalation, which  
37 is preferred. The effective dose of compound depends

01  
02 on the particular compound employed, the condition of  
03 the patient and the frequency and route of  
04 administration, but in general is in the range of from  
05 0.001 mg/day to 100 mg/day per kilogram of the  
06 patient's body weight.

07  
08 Where appropriate, small amounts of other  
09 antilasthmatics and bronchodilators, for example  
10 sympathomimetic amines such as isoprenaline,  
11 isoetharine, salbutamol, phenylephrine and ephedrine;  
12 xanthine derivatives such as theophylline and  
13 aminophylline and corticosteroids such as prednisolone  
14 and adrenal stimulants such as ACTH may be included.

15  
16 For use in treatment of inflammatory diseases, a  
17 preparation of the invention will preferably be in a  
18 form suitable for oral administration, for example a  
19 tablet or capsule or a sachet containing  
20 reconstitutable powder. A unit dose will generally  
21 contain from 20 to 1000 mg and preferably will contain  
22 from 30 to 500 mg, in particular 50, 100, 150, 200,  
23 250, 300, 350, 400, 450, or 500 mg. The preparation  
24 may be administered once or more times a day for  
25 example 2, 3 or 4 times daily, and the total daily dose  
26 for a 70 kg adult will normally be in the range 100 to  
27 3000 mg. Alternatively the unit dose will contain from  
28 2 to 20 mg of active ingredient and be administered in  
29 multiples, if desired, to give the preceding daily  
30 dose.

31  
32 For treatment of disorders related to the loss of  
33 gastro-intestinal integrity, a unit dose will normally  
34 contain 1 to 2000 mg, for example 5 to 1000 mg, of the  
35 active ingredient. Unit doses will normally be  
36 administered at least once a day, for example 1, 2, 3, 4, 5  
37 or 6 times a day such that the total daily dose is

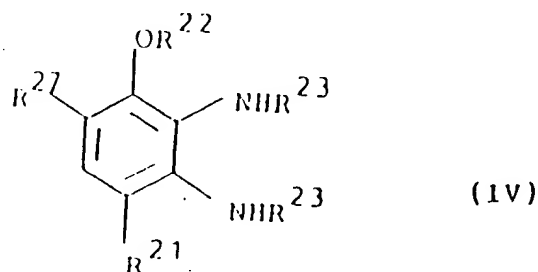
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normally in the range of 0.1 to 30 mg/kg body weight per day, e/g. 7 to 2000 mg/day for a 70 kg human adult.

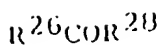
For treatment of all the above-mentioned disorders, the compositions may contain from 0.1% by weight to 99% by weight, preferably from 10 to 60% by weight, of the active ingredient, depending on the method of administration.

The present invention also provides a method of treatment which comprises administering a physiologically tolerable compound of the formula or a physiologically tolerable salt thereof to a human or animal body.

The present invention also provides a process for the manufacture of a compound of the formula I, or formula III, wherein a compound of the formula IV

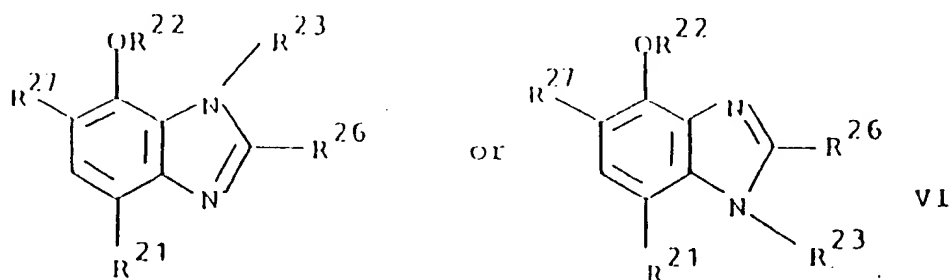


wherein R<sup>21</sup> represents hydrogen or a lower alkyl group, or a group or atom convertible thereto, R<sup>22</sup> represents hydrogen or a lower alkyl group, or a group or atom convertible thereto, one R<sup>23</sup> represents hydrogen and the other R<sup>23</sup> represents hydrogen or a lower alkyl group, or a group or atom convertible thereto, and wherein R<sup>27</sup> represents hydrogen, halogen, or alkyl, or a group or atom convertible thereto, is reacted with a compound of formula V.



V

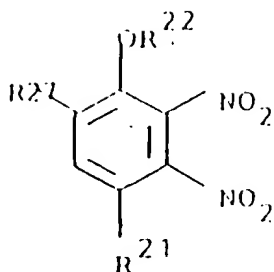
wherein  $R^{26}$  represents  $-(CR^4R^5)_n-R^6$ , or a group convertible thereto, wherein  $R^4$ ,  $R^5$ , and  $R^6$ , and  $n$  each have the meanings given above with reference to formula I or formula III and  $R^{28}$  represents a leaving group or hydrogen to form a compound of the formula VI:



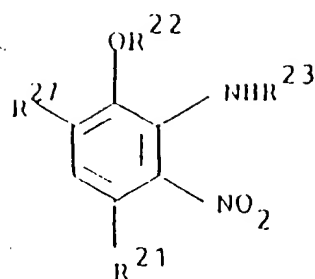
and, if required, a nitrogen atom of, and/or the 4-oxygen atom on, the benzimidazole nucleus is acylated with a group of the formula  $\overset{O}{\parallel}CR^8$  or is alkylated, and if required protecting groups are removed, to form a compound of the formula I or formula III, and if required forming a salt or solvate thereof.

Preferably any such salt or solvate is pharmaceutically acceptable. However salts or solvates which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or the compounds per se.

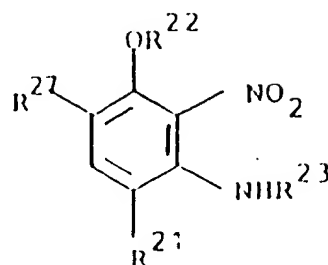
The present invention also provides a process for the manufacture of a compound of the formula I or formula III wherein the compound of formula IV is obtained by reducing a compound of the formula VII



VII



or



wherein  $R^{21}$ ,  $R^{22}$  and  $R^{23}$  and  $R^{27}$  have the meanings given above in relation to formula IV, and if desired or required protective groups are removed to form the compound of the formula IV.

Compounds of the Formula VII in which an  $R^{23}$  group represents alkyl may be made, in the case of such an  $R^{23}$  group meta to the  $OR^{22}$  group, for example by nitration in the meta position, reduction of the nitro group, monoalkylating the amino group, and nitrating in the ortho position.

The compounds in which the alkyl  $R^{23}$  group is ortho to the  $OR^{22}$  group may be made, for example, by treating the ortho, meta dinitro compound with an amine of the formula  $R^{23}NH_2$ , which preferentially replaces the ortho nitro group.

Reduction of a compound of the formula VII may be effected by conventional chemical methods or preferably by catalytic methods. Catalytic reduction, using for example palladium on charcoal or Raney nickel, is conveniently effected in a conventional hydrogenation solvent, such as a lower alkanol, e.g., ethanol. When  $R^{22}$  represents hydrogen, it may be protected by a benzyl group, introduced by, for example, heating with a benzyl halide/ $K_2CO_3$ /KI or NaI system in acetone or by a methyl group, introduced by  $CH_3I/K_2CO_3$  in acetone.

Reaction of a compound of the formula IV, whether resulting from manufacture by reduction of a compound of the formula VII and, if desired or required, removal of protecting groups, or otherwise obtained, within a compound of the formula V, is preferably effected by heating with a compound of the formula V



wherein  $R^{28}$  represents a leaving group. For example the compound may be an acid, acid chloride, acid anhydride, including a mixed anhydride of the acid  $R^{26}COOH$  and haloformate ester. The presence of an acid catalyst, e.g., HCl, may be necessary.

A compound of the formula VIII





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may react with compounds of the formula IV under the conditions of U.S. Pat. 3,282,000, 1967, 17, 55 when R<sup>26</sup> is an aryl group. Further generally applicable methods of benzimidazole synthesis are described in Chem Revs, 1974, 74(3), 279.

Removal of protecting groups if desired or required may be effected by methods known per se, for example heating with HBr or aqueous hydrochloric acid to remove a methyl protecting group or catalytic hydrogenation to remove the benzyl group, using, for example, palladium/charcoal as catalyst.

The invention further provides a process in which one compound of the formula I is converted to another compound of the formula I.

The present invention in particular provides a process for preparing a compound of the formula I in which R<sub>3</sub>

represents  $\overset{\text{O}}{\parallel}\text{CR}^8$  which comprises treating a compound of the formula I in which R<sup>3</sup> represents H with an appropriate acylating agent. If R<sup>2</sup> represents hydrogen, it is desirably protected, as by a benzyl group, during the reaction. Advantageously, the reaction employs the appropriate acyl halide, preferably the chloride, and is carried out in basic conditions using, for example, triethylamine and chloroform as the medium.

The present invention further provides a process for the manufacture of an ester of a compound of the formula I, which comprises acylating a compound of the formula I in which R<sub>2</sub> represents hydrogen, under conditions preventing or inhibiting acylation of the N-atoms of the benzimidazole nucleus, for example in a

01 trifluoroacetic acid medium, other reactive groups in  
02 the molecule being blocked by a protective group where  
03 necessary. The acylation preferably attaches a group  
04

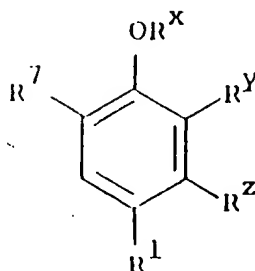
05 of the formula  $\overset{\text{O}}{\underset{\text{H}}{\text{C}}} \text{R}^8$  to the oxygen atom at the  
06 2-position.  
07

08  
09 Compounds of the formula I in which  $\text{R}^7$  is other than  
10 hydrogen may be made by methods known per se. For  
11 example, a compound in which  $\text{R}^7$  represents halogen,  
12 e.g., bromine or chlorine, may be prepared by  
13 halogenating phenol, if desired p-substituted as by  
14 alkyl, in the 2-position followed by sequential  
15 nitration in the 5 and 6 positions, the phenolic  
16 hydrogen being protected at the required stages. A  
17 similar procedure may be used when  $\text{R}^7$  represents an  
18 alkyl group; subsequent reduction to the diamino  
19 precursor of formula IV and its conversion to the  
20 benzimidazole of formula I may be effected as described  
21 above.  
22

23 Reaction schemes for the preparation of 5-substituted  
24 benzimidazoles and of compounds of the formula VII in  
25 which one  $\text{R}^{23}$  does not represent hydrogen are given  
26 below by way of illustration only.  $\text{R}^1$ ,  $\text{R}^{21}$ ,  $\text{R}^{27}$  and  
27  $\text{R}^{26}$  have the meanings given above in relation to  
28 formula I (or formula III) IV, IV and V respectively,  
29  $\text{R}^1$  preferably being methyl. Certain of the  
30 intermediates are novel, and the present invention also  
31 provides these compounds, and the process for their  
32 manufacture herein described.  
33

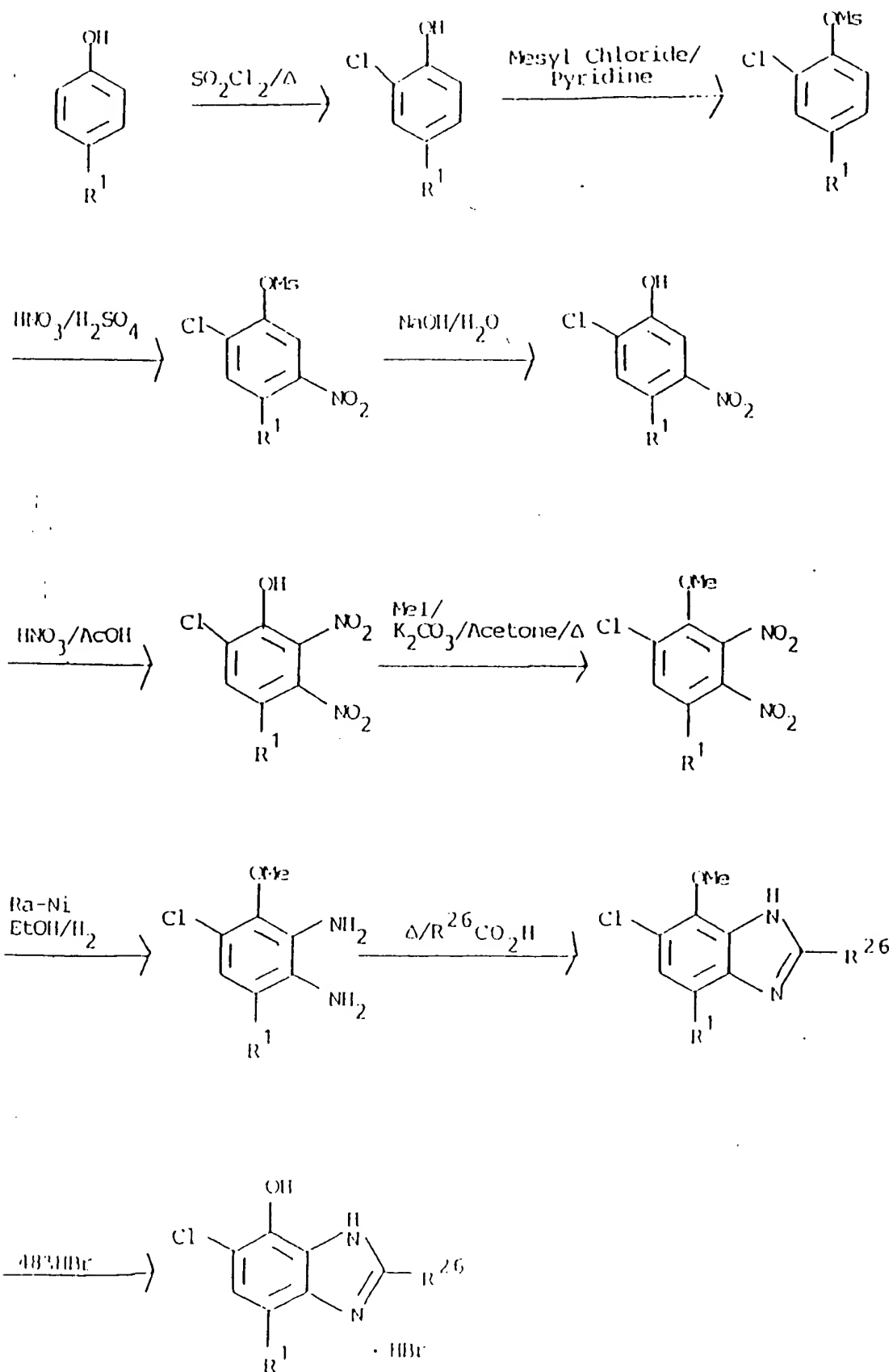
- 18 -

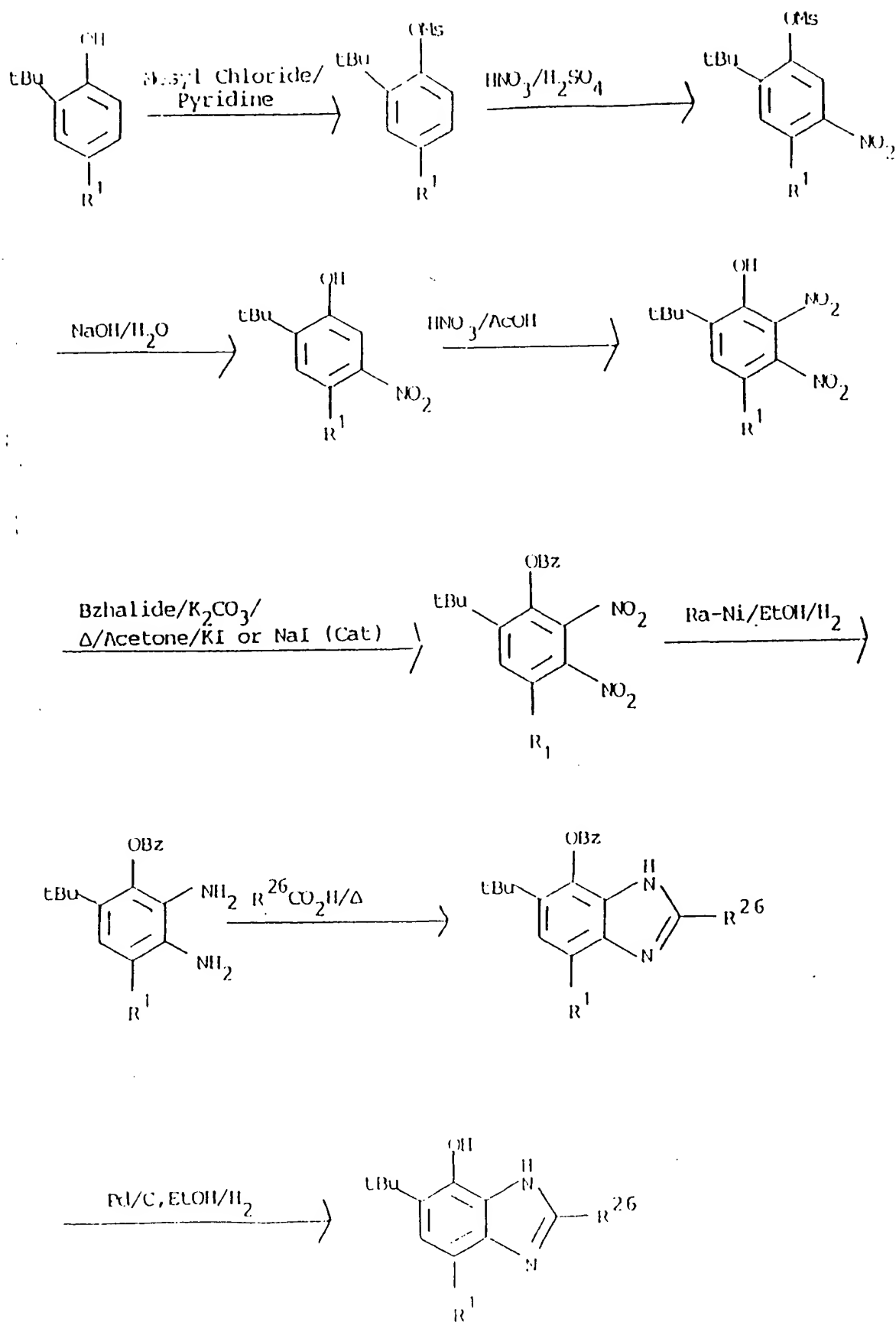
In particular the present invention provides novel intermediates of the formula IX:

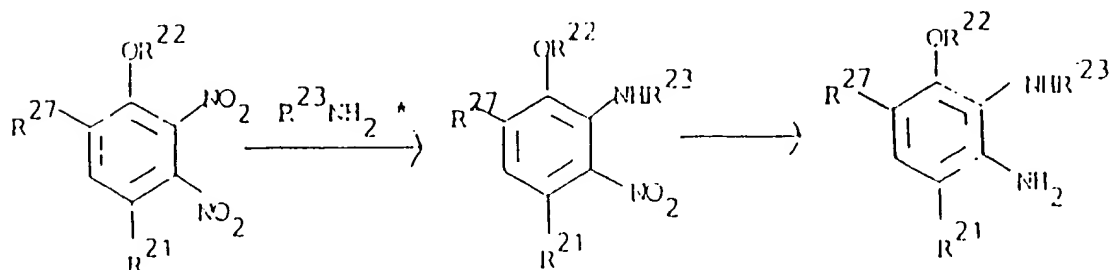
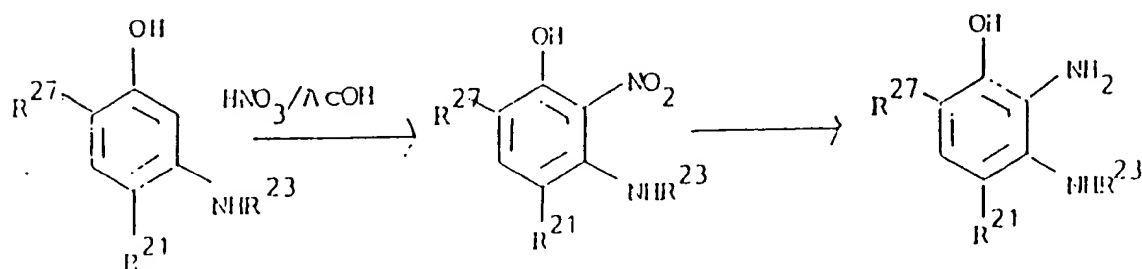
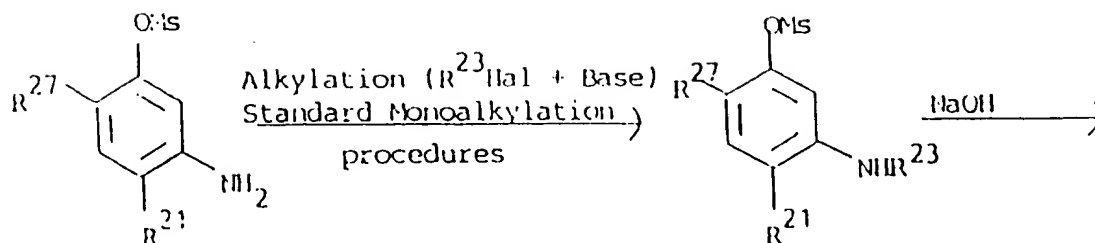
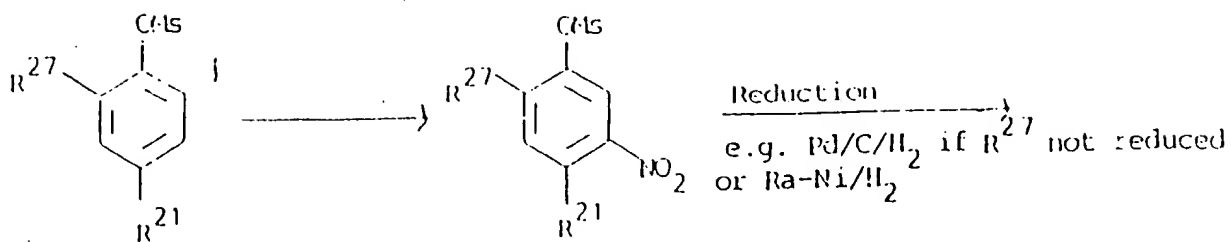


(IX)

in which  $R^1$  is as defined for formula I,  $R^X$  is benzyl or mesyl or  $R^2$  as defined for formula I,  $R^Y$  is hydrogen,  $NO_2$  or  $NH_2$ , and  $R^Z$  is  $NO_2$  or  $NH_2$ , and  $R^7$  is tert. butyl.

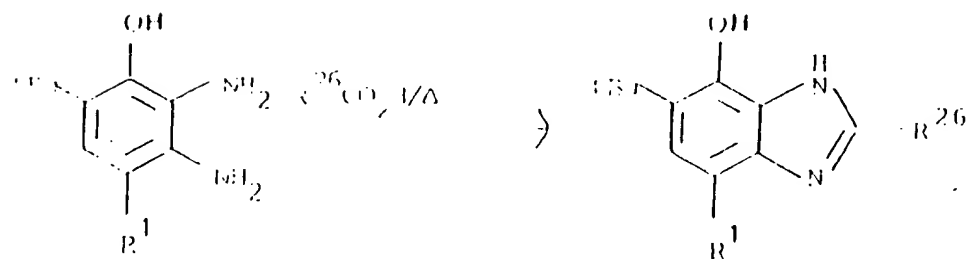
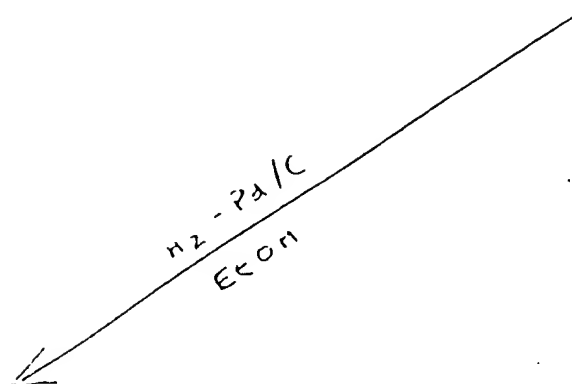
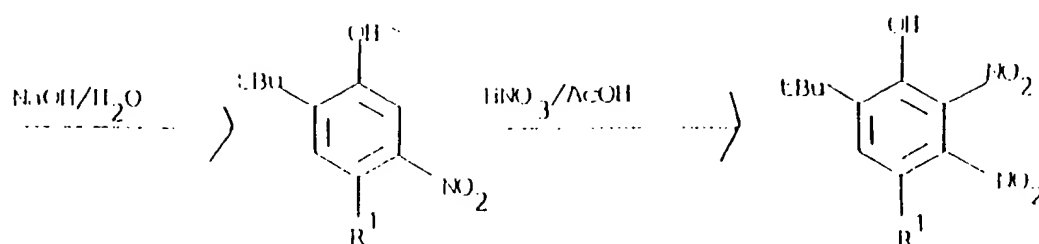
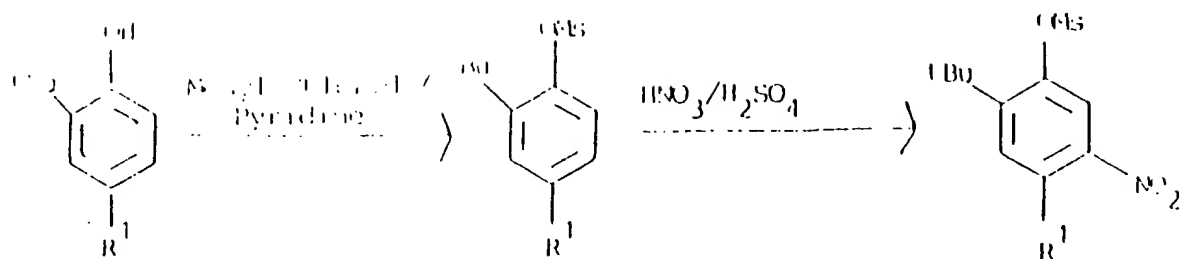






\* see J.F. Bunnett and R.E. Zahler, Chem. Rev. 1951, 49, 254

R.E. Markwell, Chem. Commun. 1979, 428

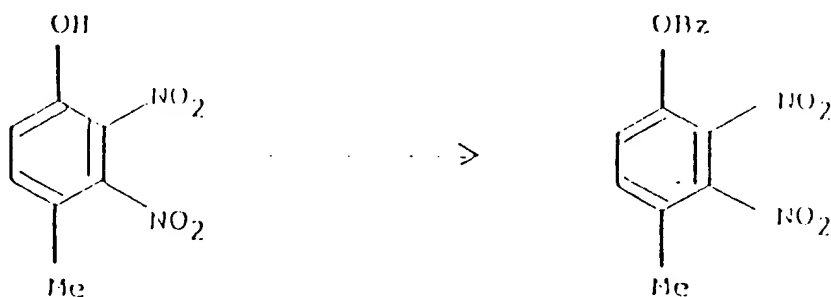


The present invention also provides a process for the manufacture of a pharmaceutical preparation of a compound of the formula I, which comprises preparing a physiologically tolerable compound of the formula I, advantageously by the reaction of a compound of the formula IV with a compound of the formula V, the compound of the formula IV preferably having been made by reduction of the nitro groups in a compound of the formula VII to amine groups, and if required removing protecting groups, and if required forming a physiologically tolerable salt thereof, and admixing the physiologically tolerable compound or salt with a pharmaceutically acceptable excipient.

The following descriptions illustrate the preparation of intermediates for the compounds of the invention. The following examples illustrate the invention:

#### DESCRIPTION 1

##### 4-Benzyloxy-2,3-dinitrotoluene



A mixture of 4-methyl-2,3-dinitrophenol<sup>1</sup> (12.0g), anhydrous potassium carbonate (15g), potassium iodide (0.1 g), benzyl chloride (25 g) in acetone (A.R., 150 ml) was heated and stirred under reflux for 18 hr.



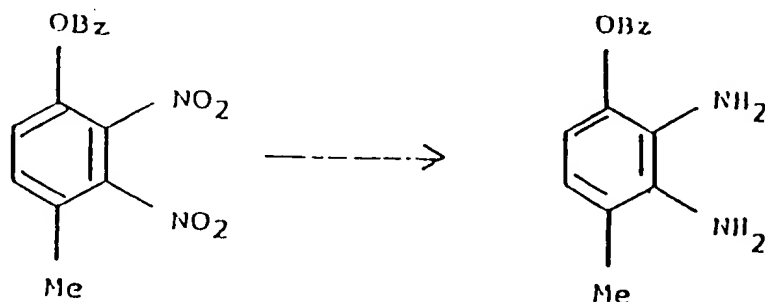
- 24 -

The mixture was cooled, filtered, and the filtrate evaporated to dryness in vacuo. The residue was taken up in chloroform (400 ml) and washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to half volume in vacuo. Addition of pentane (150 ml) gave the title compound, 16.2g, (93%) m.p. 116-118°C.

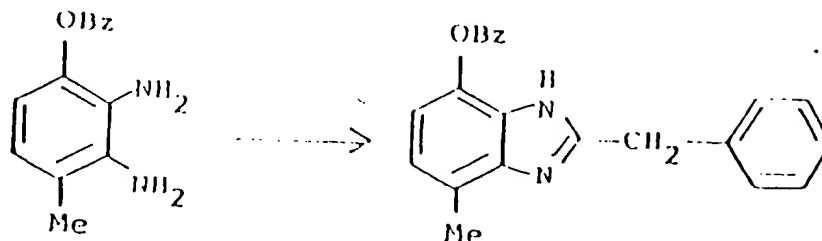
M.F.Dadswell and J.Kenner, J.Chem. Soc. 580 (1927).

DESCRIPTION 2

2,3-Diamino-4-benzyloxytoluene



4-Benzyloxy-2,3-dinitrotoluene (7 g), in ethanol and Raney-nickel (3 g), was hydrogenated at room temperature and pressure until uptake of hydrogen ceased (3 h). The colourless solution was filtered (celite) and evaporated to dryness in vacuo to afford the title compound as an unstable oil, (5 g), which was used immediately for the next step.

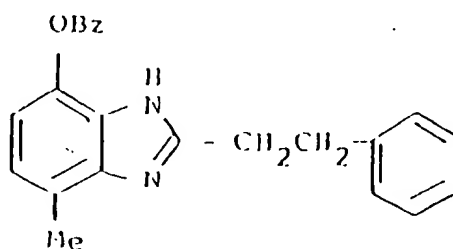
DESCRIPTION 32-Benzyl-4-benzyloxy-7-methylbenzimidazole

A mixture of 2,3-diamino-4-benzyloxytoluene (5 g) and phenylacetic acid (23 g) was heated at 120°C for 1 h. The mixture was cooled, dissolved in chloroform and washed with 10% sodium carbonate solution, and then with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to dryness in vacuo. The residue was recrystallized from ethyl acetate-hexane to afford the title compound, (4.4 g), m.p. 198-200°C.

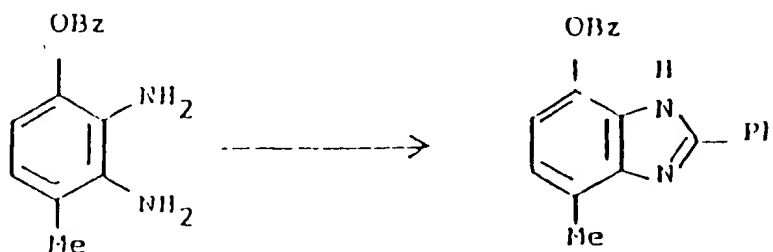
Anal: C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O requires C, 80.45; H, 6.15; N, 8.55%.

Found: C, 80.35; H, 6.05; N, 8.45%.

Similarly prepared was:

DESCRIPTION 42-Phenethyl-4-benzyloxy-7-methylbenzimidazole

m.p. 203-4°C (Ethanol).

DESCRIPTION 54-Benzyloxy-7-methyl-2-phenylbenzimidazole

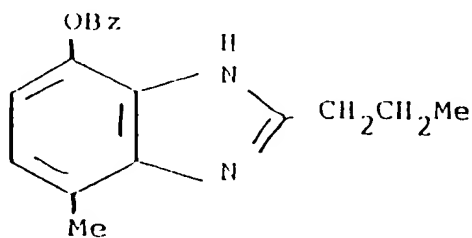
A mixture of 2,3-diamino-4-benzyloxytoluene (5.0 g) and benzaldehyde (5.52 g, 2 mol. equiv.) in xylene (75 ml) was heated under reflux for 3h, and then left for 18 h at room temperature. The resulting crystalline product was filtered, washed with ether, and recrystallized from ethanol to afford the title compound, 4.13g, m.p. 221-224°C.

Anal:  $C_{21}H_{18}N_2O$  requires C, 80.25; H, 5.75; N, 8.9%  
Found: C, 80.15; H, 5.60; N, 8.8%

Similarly prepared was

DESCRIPTION 6

2-n-Propyl-4-benzyloxy-7-methylbenzimidazole



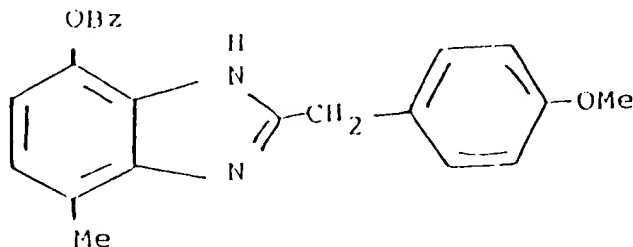
m.p. 192-194°C (ethanol-ethyl acetate).

Anal:  $C_{18}H_{20}N_2O$  requires C, 77.11; H, 7.19; N, 9.99%.

Found: C, 76.85; H, 7.19; N, 9.91%.

DESCRIPTION 7

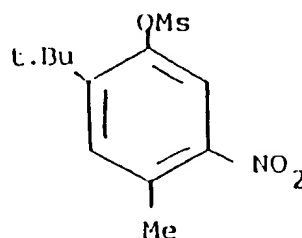
2-(4'-Methoxybenzyl)-4-benzyloxy-7-methylbenzimidazole



m.p. 181-183°C (ethyl acetate).  
Anal:  $C_{23}H_{22}N_2O_2$  requires C, 77.07; H, 6.19; N, 7.82%.  
Found: C, 77.22; H, 6.26; N, 7.81%.

DESCRIPTION B

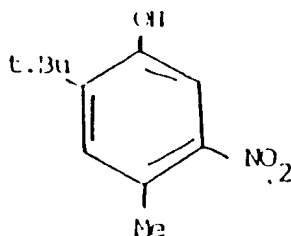
2-Nitro-4-hydroxy-5-tert-butyltoluene-O-mesylate



Mesyl chloride (147 g) was added dropwise over 0.5 h to a solution of 3-tert-butyl-4-hydroxytoluene (200 g) in pyridine (500 ml) at 0°C. The solution was stirred at 10°C for 1 h and then at room temperature for a further 3 h. It was poured into excess 5N-hydrochloric acid and extracted with dichloromethane. The organic layer was washed with 5N-hydrochloric acid, water and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation to dryness in vacuo afforded crude 3-tert-butyl-4-hydroxytoluene-O-mesylate (250 g) which was dissolved in concentrated sulphuric acid (750 ml) and cooled to 0°C. A mixture of concentrated nitric acid (93 g) and concentrated sulphuric acid (175 ml) was added dropwise over 1 h maintaining the temperature at 0°C. The solution was poured onto ice, and the resulting solid was collected, washed with water and air-dried to afford the title compound (260 g), m.p. 69-78°C sufficiently pure for the next step. A portion was recrystallised from chloroform-pentane, m.p. 91-92°C.

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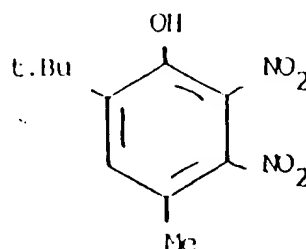
Anal:  $C_{12}H_{17}NO_5S$  requires C, 50.16; H, 5.96; N, 4.87%.  
Found: 49.98; H, 5.98; N, 4.85%.

DESCRIPTION 92-Nitro-4-hydroxy-5-tert-butyltoluene

The crude product from Description 8 (260 g) was stirred with a solution of sodium hydroxide (130 g) in water (800 ml) at 60-70°C until all the solid had dissolved (1.5 h). The solution was filtered and poured onto an excess of ice and 5N hydrochloric acid. The mixture was extracted with dichloromethane and the organic layer was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation to dryness in vacuo afforded the title compound (140 g) sufficiently pure for the next step.

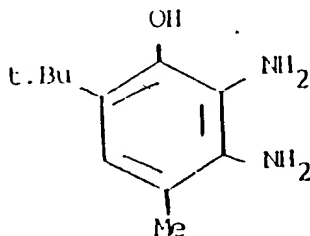
A portion was recrystallised from dichloromethane-pentane, m.p. 96-98°C.

Anal:  $C_{11}H_{15}NO_3$  requires C, 63.4; H, 7.23; N, 6.69%.  
Found: C, 63.22; H, 7.2; N, 6.69%.

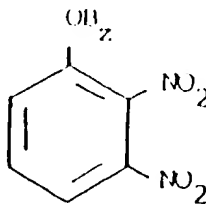
DESCRIPTION 192,3-Dinitro-4-hydroxy-5-tert-butyltoluene

A solution of fuming nitric acid (10.02 ml) in acetic acid (15 ml) was added dropwise over 15 min to a solution of the crude product from Description 9 (35 g) in acetic acid (60 ml) while maintaining the temperature at 18-20°C. After a further 10 min the solution was poured onto ice and the resulting solid was collected and washed with water. It was dissolved in dichloromethane, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The product was purified by column chromatography on Silica Gel 60 (250 g) eluting with dichloromethane. Recrystallisation from dichloromethane-pentane afforded the title compound (25 g), m.p. 104-105°C.

Anal: C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub> requires C, 51.97; H, 5.55; N, 11.02%.  
Found: C, 51.88; H, 5.62; N, 11.00%.

DESCRIPTION 112,3-Diamino-4-hydroxy-5-tert-butyltoluene

A solution of 2,3-dinitro-4-hydroxy-5-tert-butyltoluene (Description 10) (7.5 g) in ethanol (350 ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium-carbon (2.5 g) until uptake of hydrogen ceased. The solution was filtered under nitrogen and evaporated to dryness in vacuo to afford the unstable title compound, m.p. 125-136°C, which was used immediately for the next reaction.

DESCRIPTION 12O-Benzyl-2,3-dinitrophenol



A mixture of 2,3-dinitrophenol<sup>1</sup> (10.0 g), anhydrous potassium carbonate (11.0 g) and benzyl chloride (8.22 g) in acetone (250 ml) was heated under reflux for 8 h. The solution was filtered and the filtrate evaporated to dryness in vacuo.

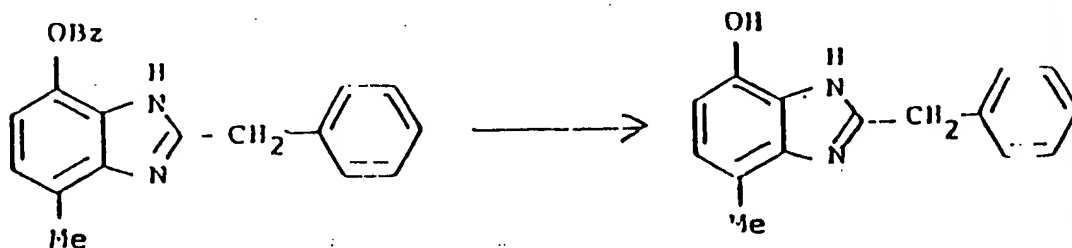
The residue was re-crystallised from chloroform-hexane to afford the title compound (14.2 g), m.p. 100-101°C.

#### Reference

1 A. Bantlin, Berichte, 11, 2104, (1878).

#### EXAMPLE 1

#### 2-Benzyl-4-hydroxy-7-methylbenzimidazole



A solution of 2-benzyl-4-benzyloxy-7-methylbenzimidazole (3.0 g) in ethanol (400 ml) and 10% palladium-carbon (1.5 g) was hydrogenated at room temperature and pressure until uptake of hydrogen ceased. The mixture was filtered (celite), and the filtrate was evaporated to dryness in vacuo and recrystallized from ethanol-ether to afford the title compound (1.85 g), m.p. 204-205°C.

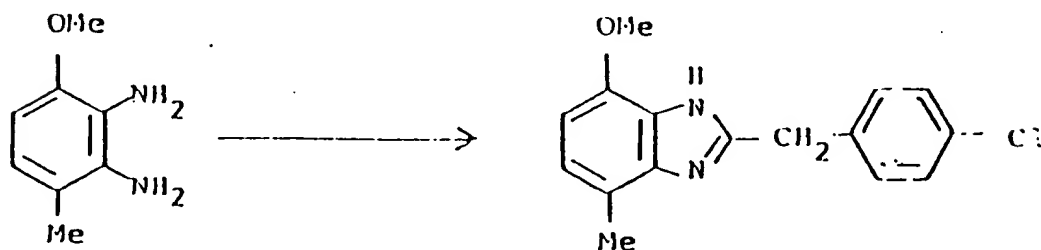
Anal:  $C_{15}H_{14}N_2O$  requires C, 75.6; H, 5.9; N, 11.75%.

Found: C, 75.35; H, 5.85; N, 11.7%.

$\delta[(CD_3)_2SO]$	2.4 (3H, s)
	4.2 (2H, s)
	6.45 (1H, d, $J=8Hz$ )
	6.75 (1H, d, $J=8Hz$ )
	7.3. (5H, m)
	9.6 (1H, br. s)

## EXAMPLE 2

### 2-(4-Chlorobenzyl)-4-methoxy-7-methylbenzimidazole



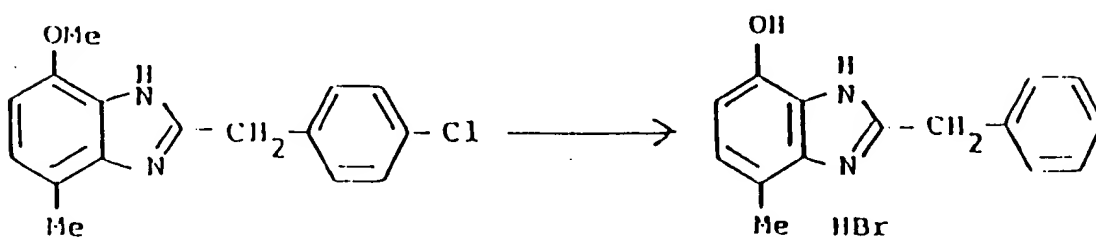
A mixture of 2,3-diamino-4-methoxytoluene [prepared by hydrogenation of 4-methoxy-2,3-dinitrotoluene (7.5 g) over 10% palladium-carbon (2.5 g) in ethanol] and 4-chlorophenylacetic acid (23 g) was heated at 130-150°C for 4.5 h under nitrogen. The mixture was cooled, dissolved in chloroform, washed with 10% sodium carbonate solution, then with water, dried ( $Na_2SO_4$ ) and evaporated to dryness in vacuo. The product was recrystallized from chloroform-pentane to afford the title compound, (5.75 g), m.p. 195-197°C.

Anal:  $C_{16}H_{15}ON_2Cl$  requires C, 67.00; H, 5.25; N, 9.75;  
Cl, 12.35%

Found: C, 67.05; H, 5.30; N, 9.85; Cl, 12.60%

EXAMPLE 3

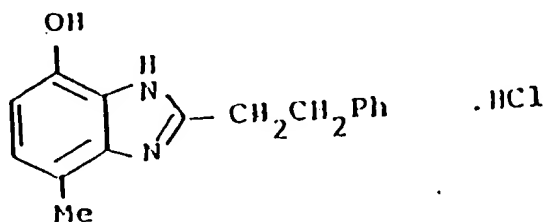
2-(4-Chlorobenzyl)-4-hydroxy-7-methylbenzimidazole  
hydrobromide



A suspension of 2-(4-chlorobenzyl)-4-methoxy-7-methylbenzimidazole (4.0 g) in 48% aqueous hydrobromic acid (400 ml) under nitrogen was heated at  $130^{\circ}$  for 5 h, then evaporated to dryness in vacuo. The residue was recrystallized from ethanol-ether to afford the title compound (3.95 g), m.p.  $275-277^{\circ}C$ .

Anal:  $C_{15}H_{13}ON_2Cl \cdot HBr$ . requires C, 50.95; H, 4.0; N, 7.9%  
Found: C, 50.60; H, 3.9; N, 7.8%

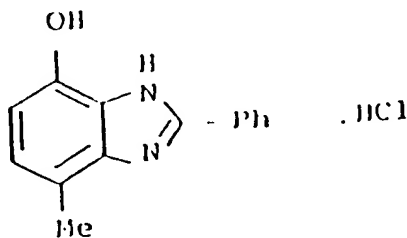
After preparing the free base in a manner similar to that described in Example 1, the following were prepared by the addition of ethereal hydrogen chloride to a solution of the free base in ethanol-ether.

EXAMPLE 42-Phenethyl-4-hydroxy-7-methylbenzimidazole  
hydrochloride

m.p. 238-40°C.

Anal: C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>OHCl requires C, 66.55; H, 5.93; N, 9.70%;

Found: C, 66.71; H, 5.96; N, 9.67%

EXAMPLE 52-Phenyl-4-hydroxy-7-methylbenzimidazole hydrochloride

m.p. 252-6°C (dec).

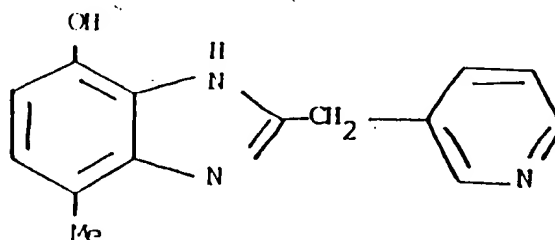
Anal: C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>OHCl requires C, 64.5; H, 5.00; N, 10.75;

Cl, 13.60%

Found: C, 64.2; H, 4.85; N, 10.55; Cl, 13.55%

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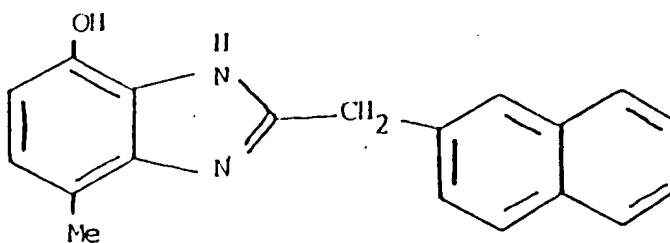
Prepared in an analogous manner were:

EXAMPLE 62-(Pyrid-3-yl)methyl-4-hydroxy-7-methylbenzimidazole

m.p. 264-268°C (methanol/ethylacetate/ether)

Anal:  $C_{14}H_{13}N_3O$  requires C, 70.28; H, 5.48; N, 17.56%.

Found: C, 70.15; H, 5.62; N, 17.23%.

EXAMPLE 72-(Naphth-2-ylmethyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride

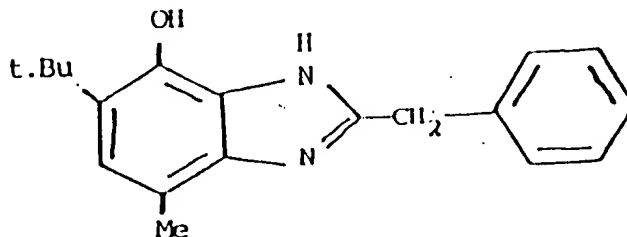
.HCl

m.p. &gt;230°C (dec)

Anal:  $C_{19}H_{16}N_2O \cdot HCl$  requires C, 70.25; H, 5.28;

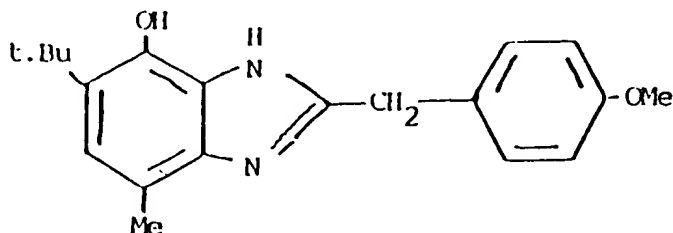
N, 8.63; Cl, 10.92%.

Found: C, 70.41; H, 5.31; N, 8.59; Cl, 11.04%.

EXAMPLE 82-Benzyl-4-hydroxy-5-tert-butyl-7-methylbenzimidazole

A mixture of 2,3-diamino-4-hydroxy-5-tert-butyltoluene (Description 11) (prepared from 12 g of 2,3-dinitro-4-hydroxy-5-tert-butyltoluene) and phenylacetic acid (30 g) was heated for 1 h at 120-130°C under nitrogen. The reaction product was extracted with chloroform, washed with 10% sodium carbonate, water, and dried (Na<sub>2</sub>SO<sub>4</sub>). The chloroform solution was evaporated to dryness in vacuo, and recrystallise from chloroform-ethylacetate-pentane to afford the title compound (9.3 g), m.p. 226-228°C.

Anal: C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O requires C, 77.52; H, 7.53; N, 9.52%.  
Found: C, 77.31; H, 7.64; N, 9.76%.

EXAMPLES (9a) AND (9b)5-tert-Butyl-4-hydroxy-2-(4'-methoxybenzyl)-7-methyl-  
benzimidazole (9a) and the hydrochloride salt (9b)

Example 9a Free Base

Example 9b HCl

The title compound (9a) was prepared in an analogous manner to Example 8. m.p. 269-270°C (ethanol/ether)

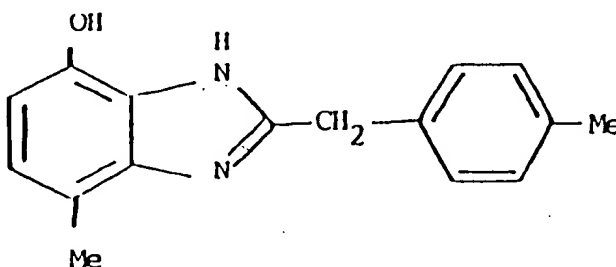
The free base (9a) was treated with ethanolic-hydrogen chloride to afford the hydrochloride salt (Example 9b). m.p. 232-235°C (ethanol/ether).

Anal: C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> HCl requires C, 66.56; H, 6.98; N, 7.76; Cl, 9.82%.

Found: C, 66.58; H, 7.06; N, 7.79; Cl, 10.00%.

EXAMPLE 102-(4'-Methylbenzyl)-4-hydroxy-7-methylbenzimidazole

This compound was prepared in a analogous manner to Example 1.

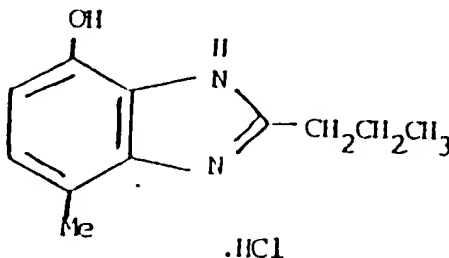


m.p. 217-8°C.

Anal:  $C_{16}H_{16}N_2O$  requires C, 75.86; H, 6.30; N, 11.04%.

Found: C, 75.25; H, 6.37; N, 11.06%.

The following were prepared in an analogous manner to Example 4.

EXAMPLE 112-n-Propyl-4-hydroxy-7-methylbenzimidazole  
hydrochloride

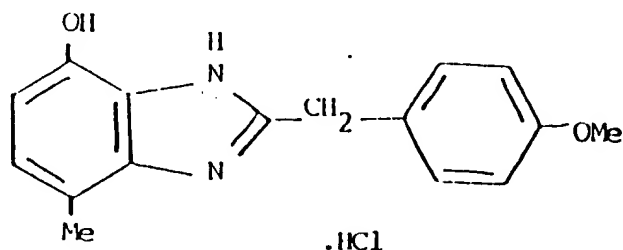


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02 m.p. 204-206°C (ethanol/ethyl acetate/ether)  
 03 Anal:  $C_{11}H_{14}N_2O \cdot HCl$  requires C, 58.27; H, 6.66;  
 04 N, 12.35; Cl, 15.63%.  
 05 Found: C, 58.25; H, 6.97; N, 12.30; Cl, 15.79%.

08 EXAMPLE 12

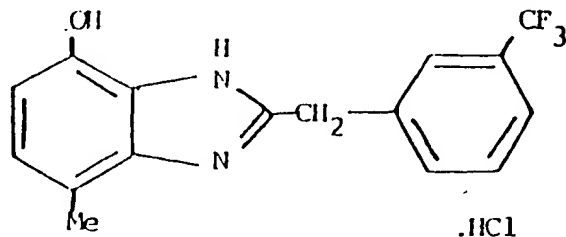
09  
 10 2-(4'-Methoxybenzyl)-4-hydroxy-7-methylbenzimidazole  
 11 hydrochloride



20 m.p. 228-229°C (ethanol-water)  
 21 Anal:  $C_{16}H_{16}N_2O_2 \cdot HCl$  requires C, 63.05; H, 5.62;  
 22 N, 9.19; Cl, 11.63%.  
 23 Found: C, 62.95; H, 5.88; N, 9.08; Cl, 11.68%.

24  
 25 EXAMPLE 13

26  
 27 2-(3'-Trifluoromethylbenzyl)-4-hydroxy-7-methylbenzimi-  
 28 dazole hydrochloride

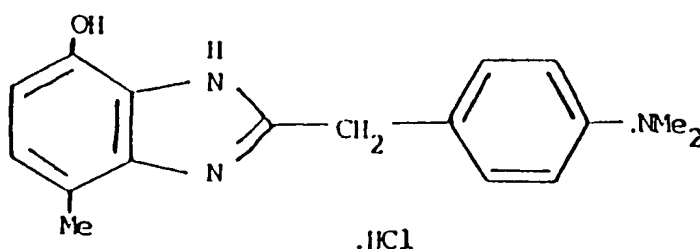


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m.p. &gt;280°C (dec)

Anal:  $C_{15}H_{11}F_3N_2O \cdot HCl$  requires C, 54.80; H, 3.68;  
N, 8.52; Cl, 10.79%.

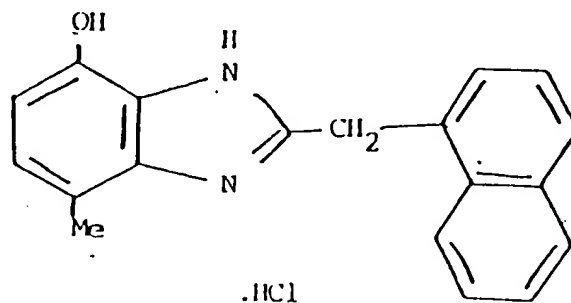
Found: C, 54.58; H, 3.62; N, 8.45; Cl, 10.50%.

EXAMPLE 142-(4'-N,N-dimethylaminobenzyl)-4-hydroxy-7-methylbenzimidazole hydrochloride

m.p. 175-194°C.

Anal:  $C_{17}H_{19}N_3O \cdot HCl$  requires C, 63.26; H, 5.97;  
N, 13.81; Cl, 11.67%.

Found: C, 63.25; H, 5.99; N, 13.40; Cl, 11.6%.

EXAMPLE 152-(Naphth-1-ylmethyl)-4-hydroxy-7-methylbenzimidazole hydrochloride

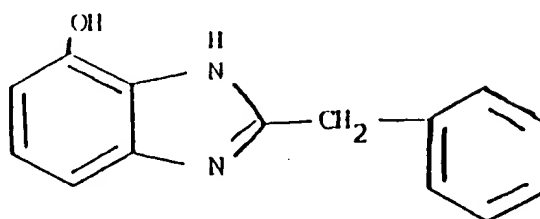
m.p. 262-3°C.

Anal:  $C_{19}H_{16}N_2O \cdot HCl$  requires C, 70.26; H, 5.28; N, 8.63; Cl, 10.92%.

Found: C, 70.36; H, 5.32; N, 8.57; Cl, 11.49%.

EXAMPLE 16

2-Benzyl-4-hydroxybenzimidazole



A solution of O-benzyl-2,3-dinitrophenol (Description 12) (4.5 g) in ethanol (300 ml) was hydrogenated at atmospheric pressure over Raney nickel (2 g) until uptake of hydrogen ceased. The solution was filtered and evaporated to dryness in vacuo to afford unstable O-benzyl-2,3-diaminophenol which was immediately heated with phenylacetic acid (20 g) at 140-150°C for 3 h. The product was heated under reflux with 5N-hydrochloric acid (70 ml) for 3 h and neutralised with 10% sodium carbonate. The mixture was extracted with chloroform, and the organic layer washed with 10% sodium carbonate, water and dried ( $Na_2SO_4$ ). The recovered product was chromatographed on Silica Gel 60 (250 g) eluting with ethylacetate-chloroform (1:19) to afford the title compound (1.6 g), m.p. 172-174°C (ethanol/ether).

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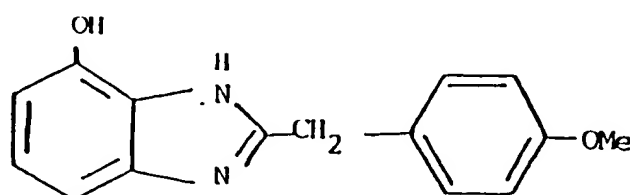
Anal:  $C_{14}H_{12}N_2O$  requires C, 74.98; H, 5.39; N, 12.49%.

Found: C, 75.39; H, 5.36; N, 12.6%.

Similarly prepared was

EXAMPLE 17

2-(4'-Methoxybenzyl)-4-hydroxybenzimidazole  
hydrochloride



.HCl

m.p. 194-196°C (methanol/ether)

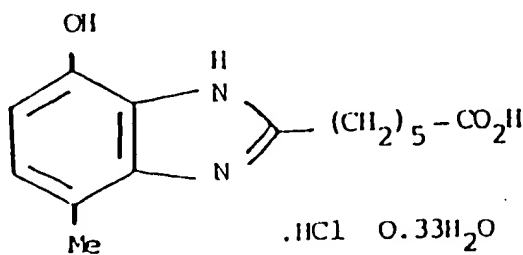
Anal:  $C_{15}H_{14}N_2O_2HCl$  requires C, 61.75; H, 5.52;

N, 9.60%.

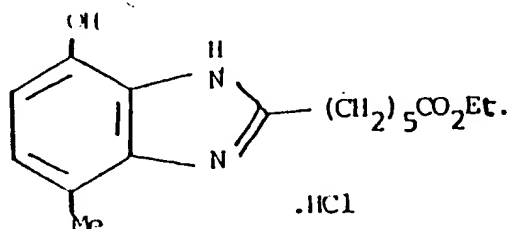
Found: C, 61.91; H, 5.25; N, 9.58%.

EXAMPLE 18

6-(4-Hydroxy-7-methyl-benzimidazol-2-yl)-hexanoic acid  
hydrochloride hydrate (3:3:1)



.HCl 0.33H<sub>2</sub>O

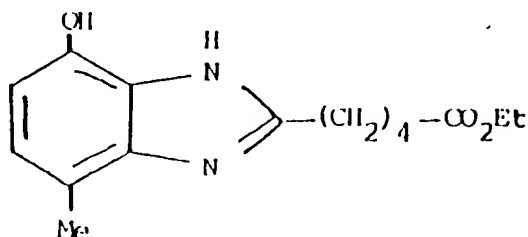
EXAMPLE 19Ethyl6-(4-hydroxy-7-methyl-benzimidazol-2-yl)-hexanoate  
hydrochloride

The compound of Example 18 (1.95 g) was heated under reflux in dry ethanol (100 ml) containing 5 drops conc. hydrochloric acid, for 0.5 h under nitrogen, and then evaporated to dryness in vacuo. The product was recrystallised from ethanol/ether to afford the title compound (1.99 g), m.p. 144-146°C.

Anal:  $C_{16}H_{22}N_2O_3.HCl$  requires C, 58.5; H, 7.09; N, 8.57; Cl, 10.84%.

Found: C, 58.59; H, 7.00; N, 8.3; Cl, 10.97%.

Similarly prepared were

EXAMPLE 20Ethyl 5-(4-hydroxy-7-methyl-benzimidazol-2-yl)-  
pentanoate

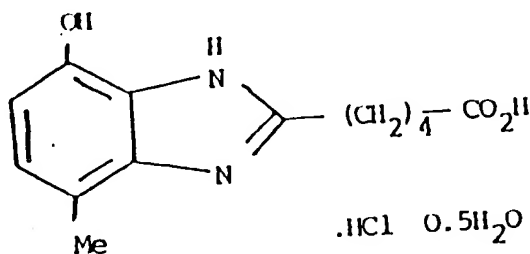
m.p. 133-135°C (ether)

Anal:  $C_{15}H_{20}N_2O_3$  requires C, 65.20; H, 7.30; N, 10.15%.

Found: C, 64.95; H, 7.13; N, 9.96%.

#### EXAMPLE 21

5-(4-Hydroxy-7-methyl-benzimidazol-2-yl)-pentanoic acid  
hydrochloride hemihydrate



m.p. 186-191°C (water)

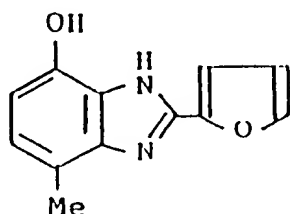
Anal:  $C_{13}H_{16}N_2O_3 \cdot HCl \cdot 0.5H_2O$  requires C, 53.13; H, 6.17; N, 9.53%.

Found: C, 53.56; H, 5.79; N, 9.46%.

The following were prepared in an analogous manner to Example 4.

#### EXAMPLE 22

2-(2'-Furyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride : Ethanol (2:1)



HCl 0.5 EtOH

0178413

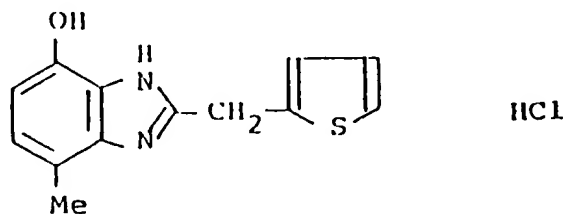
- 46 -

m.p. 256-8°C (dec). (ethanol-ether)

Anal.  $C_{12}H_{10}N_2O_2 \cdot HCl$  :  $0.5C_2H_6O$  requires C, 56.29;  
H, 5.12; N, 10.10; Cl, 14.06%. Found C, 55.95; H, 4.90;  
N, 9.91; Cl, 13.83%.

EXAMPLE 23

2-(Thien-2-ylmethyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride

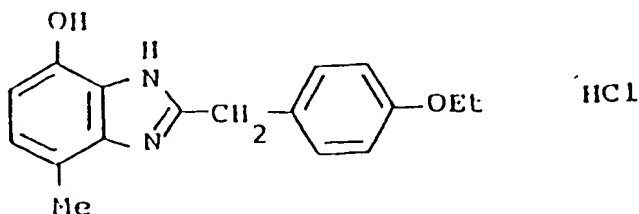


m.p. 206-8°C (ethanol-ether)

Anal.  $C_{13}H_{12}N_2OS \cdot HCl$  requires C, 55.61; H, 4.67;  
N, 9.98; S, 11.42; Cl, 12.63%. Found C, 56.22; H, 4.77;  
N, 9.72; S, 11.03; Cl, 12.63%.

EXAMPLE 24

2-(4'-Ethoxybenzyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride

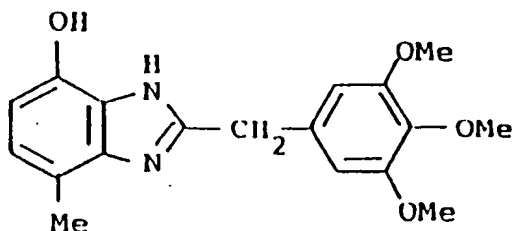


m.p. 227-90°C (ethanol-ether)

Anal.  $C_{17}H_{18}N_2O_2 \cdot HCl$  requires C, 64.05; H, 6.01;  
N, 8.79; Cl, 11.12%. Found: C, 63.98; H, 5.96; N, 8.62;  
Cl, 10.91%.

EXAMPLE 25

2-(3',4',5'-Trimethoxybenzyl)-4-hydroxy-7-methylbenzimidazole hydrochloride

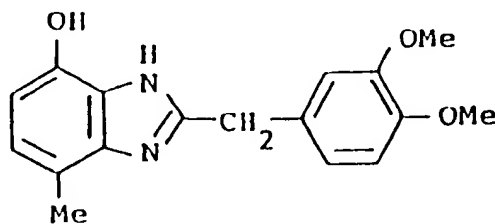


m.p. 250-1°C (dec) (ethanol-ether)

Anal.  $C_{18}H_{20}N_2O_4 \cdot HCl$  requires C, 59.26; H, 5.80;  
N, 7.68; Cl, 9.72%. Found: C, 59.06; H, 5.96; N, 7.65;  
Cl, 9.96%.

EXAMPLE 26

2-(3',4'-Dimethoxybenzyl)-4-hydroxy-7-methylbenzimidazole hydrochloride



m.p. 264-5°C (dec) (ethanol-ether)

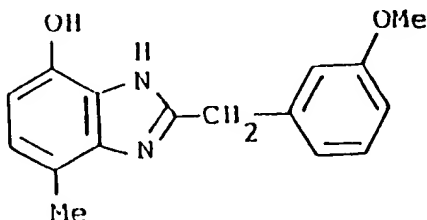


- 48 -

Anal.  $C_{17}H_{18}N_2O_3 \cdot HCl$  requires C, 60.98; H, 5.72; N, 8.37; Cl, 10.59%. Found: C, 60.69; H, 5.71; N, 8.23; Cl, 10.78%.

EXAMPLE 27

2-(3'-Methoxybenzyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride : Ethanol



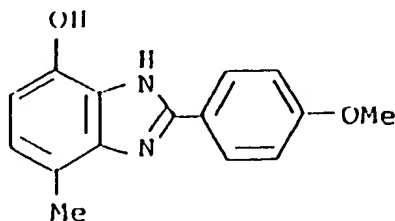
HCl. EtOH

m.p. 239-241°C (ethanol-ether)

Anal.  $C_{16}H_{16}N_2O_2 \cdot HCl \cdot C_2H_6O$  requires C, 61.62; H, 6.61; N, 7.99%. Found: C, 61.91; H, 6.70; N, 8.02%.

EXAMPLE 28

2-(4'-Methoxyphenyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride : ethanol



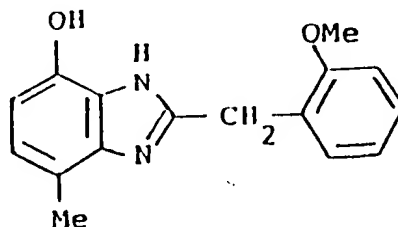
HCl. EtOH

m.p. 283-5°C (ethanol-ether)

Anal.  $C_{15}H_{14}N_2O_2 \cdot HCl \cdot C_2H_6O$  requires C, 60.44; H, 6.56; N, 8.29; Cl, 10.50%. Found: C, 60.46; H, 6.21; N, 8.31; Cl, 10.26%.

EXAMPLE 29

2-(2'-Methoxybenzyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride

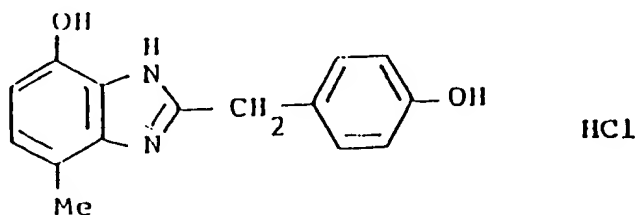


HCl

m.p. 244-245° (ethanol)

Anal:  $C_{16}H_{16}N_2O_2 \cdot HCl$  requires C, 63.05; H, 5.62; N, 9.19%.

Found: C, 63.02; H, 5.56; N, 9.24%

EXAMPLE 302-(4'-hydroxybenzyl)-4-hydroxy-7-methylbenzimidazole  
hydrochloride

m.p. 273-5°C (ethyl acetate)

Anal. C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>·HCl requires C, 61.96; H, 5.20; N, 9.64%. Found: C, 61.71; H, 5.40; N, 9.36%.

The following compounds are prepared by analogous methods:

EXAMPLE 31

2-(1-Phenylethyl)-4-hydroxy-7-methylbenzimidazole.

EXAMPLE 32

2-(Thien-2-yl)-4-hydroxy-7-methylbenzimidazole.

EXAMPLE 33

2-(Imidazol-1-yl)methyl-4-hydroxy-7-methylbenzimidazole

01  
02 EXAMPLE 34

03 2-Benzyl-3-acetyl-4-hydroxy-7-methylbenzimidazole and  
04 1-acetyl-2-benzyl-4-hydroxy-7-methylbenzimidazole.  
05

06  
07 EXAMPLE 35

08 2-Benzyl-4-hydroxy-5-chloro-7-methylbenzimidazole.  
09

10  
11 EXAMPLE 36

12 2-n-Hexyl-4-hydroxy-5-tert.-butyl-7-methylbenzimidazole  
13

14  
15 EXAMPLE 37

16 2-Benzyl-4-hydroxy-5-tert.-butyl-benzimidazole.  
17

18  
19 EXAMPLE 38

20 2-Benzyl-3-acetyl-4-hydroxy-5-chloro-benzimidazole, and  
21 1-acetyl-2-benzyl-4-hydroxy-5-chloro-benzimidazole.  
22

23 The pharmacological activity of illustrative compounds  
24 of this invention was determined using the following  
25 methods:  
26

27  
28 Method A

29  
30 Rat Adjuvant Arthritis Model

31 The test is as described by Newbould, Brit. J.  
32 Pharmacol., 1963, 21, 127-136.  
33

34 It is used to indicate anti-rheumatic activity as shown  
35 by inhibiting the development of arthritis in the rat  
36 adjuvant arthritis model.  
37  
38

The compound of Example 1 is active at a concentration of 25 mg/kg (i.p.)

#### Method B

##### RBL-1 5-Lipoxygenase Screen

5-Lipoxygenase enzyme was prepared as a 10,000 g supernatant from RBL-1 cells by the method of Jakschik [Jakschik, B.A., F.F. Sun, L.M. Lee, and M.M. Steinhoff, 1980, Biochem. Biophys. Res. Comm. 95, 103]. The 10,000 g supernatant was diluted with homogenization buffer to the equivalent of  $1.5 - 2.5 \times 10^7$  cells. ml<sup>-1</sup> and made 2mM with respect to CaCl<sub>2</sub>. Aliquots of 0.5 ml were then dispensed into tubes, and incubated at 29°C with 5 µl ethanol or compound in ethanol at the desired concentration for 2 min. Then [1-<sup>14</sup>] arachidonic acid was added in buffer to give a final concentration of 6.3 µM and 0.2 µCi per incubation, and the reaction continued at 29°C for 2 min. The reaction was terminated by adding 1 ml of acetone and cooling on ice, 0.5 ml of ice-cold saline and 10 µl of 2N formic acid were added, and the mixture was extracted with 2 x 2 ml of chloroform. The extract was stored under N<sub>2</sub> at -20°C until analysis by chromatography. Activity was measured as the percentage of total radioactivity found in 5-HETE and 5,12-diHETE, and inhibition calculated as the decrease in formation of the sum of these two species in compound-treated incubates relative to control incubates.

This test is used to show inhibition of the 5-lipoxygenase enzyme in a mammalian RBL-1 cell free 5-lipoxygenase assay.

At a 5  $\mu$ M concentration, the percentage inhibition by the compound of Example 1 was 78.1 ( $p < 0.001$ ); while at a 0.5  $\mu$ M concentration the percentage inhibition was 36.0 ( $p < 0.01$ ).

#### Method C

#### CARRAGEENIN-INDUCED PLEURISY IN THE RAT

This model of monocyte accumulation is based on the method of R. Vinegar, J.F. Truax, J.L. Selph and F.A. Voelker [Federation Proceedings 41, 2588-2595, 1982].

0.2 ml of a 2.0% solution of  $\lambda$ -carrageenin (Viscarin 402) in saline was injected intrapleurally in anaesthetised rats (wt. approx. 175-200g). Compounds were administered 1 hour before carrageenin and at 24 and 48 hours after carrageenin. 72 hours after carrageenin injection, 4.0 ml of EDTA solution (5g EDTA in 100 ml of 0.9% saline and 325 mg phenol red added together with saline to 1 litre) was injected intrapleurally after killing the animals, and the exudate removed with a syringe through the diaphragm. Exudate volume was calculated from the dilution of the phenol red injected, determined spectrophotometrically (560 nm) and cellular content estimated with a DNA assay [Karsten U. and Wollenberger A. Anal. Biochem. 77, 464-470, 1977].

This test is used to indicate anti-inflammatory activity against carrageenin-induced pleurisy in the rat.

The compound of Example 10 was active at a dose of 25mg/kg (p.o.), the compound of Example 12 at 25mg/kg (p.o.), and the compound of Example 18 at 12mg/kg (i.p.).

01

02

Method D

03

04

Rat passive peritoneal anaphylaxis (PPA)

05

06

07

08

09

10

11

12

Animals

13

14

15

16

17

18

Antiserum

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22

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36

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38

The method is essentially similar to that described previously by Ross et al (Ross, Janet W., Smith, H. and Spicer, Barbara A. Increased vascular permeability during passive peritoneal anaphylaxis in the rat. Int. Arch. Allergy appl. Immun. 51, 226, 1976.)

Charles River Sprague Dawley male rats of 225-275 g and Dunkin Hartley male white guinea pigs of 300 - 700 g were used.

Charles River Sprague Dawley male rats of 225 - 275 g were given intraperitoneal injections of 0.5 ml of either Bordetella pertussis vaccine ( $4 \times 10^{10}$  organisms/ml; Burroughs Wellcome, London) or Pertussis vaccine absorbed (not less than 41.u. B. pertussis antigen with aluminium hydroxide; The Lister Institute Elstree, England), and subcutaneous injections of 0.5ml of an emulsion of 100 mg of ovalbumin (chicken egg albumin; crystallised and lyophilised, grade V, Sigma, London) in 2ml of isotonic saline and 3ml of incomplete Freund's adjuvant. The rats were bled by cardiac puncture, under ether anaesthesia, on day 18, the blood was pooled and the serum separated, stored at  $-20^{\circ}\text{C}$  and thawed only once before use. The serum produced 72 hour passive cutaneous anaphylaxis activity in recipient rats to a dilution of 1:64 which was decreased to a dilution of less than 1:2 by heating at  $56^{\circ}\text{C}$  for 4 hours.

Passive peritoneal anaphylaxis

Rats were given intraperitoneal injections of 2 ml of a 1:5 dilution of the rat anti-serum in isotonic saline. Two hours later 0.3ml of 5% solution of Pontamine Sky Blue (Raymond A. Lamb, London) in isotonic saline was injected intravenously, followed by an intraperitoneal injection of the test compound in 1 ml of saline; (control rats received 1 ml of saline); followed 2.5 minutes later by an intraperitoneal injection of 5 ml of a Tyrode solution containing 50µg/ml heparin and 0.4 mg/ml of ovalbumin. The concentrations of the compounds were quoted as that in the 6 ml of fluid injected intraperitoneally. Exactly 5 minutes after challenge the rats were stunned and bled and their peritoneal fluids were collected by opening their peritoneal cavities over funnels into polycarbonate tubes in ice. The supernatants were separated from the cellular residue by centrifuging at 150 g for 5 minutes and any samples obviously contaminated with blood were discarded for estimation of dye, histamine and SRS-A. Groups of at least 5 rats were used for each dose of compound and the treatments were randomized.

Assay of peritoneal fluids

Collected peritoneal fluids were immediately cooled to 0°C and centrifuged and the supernatant fluids were placed in a boiling water bath for 5 minutes and stored frozen at -20°C until assayed for SRS-A.

SRS-A Assay

SRS-A was assayed on the isolated guinea pig ileum preparation in the presence of atropine ( $5 \times 10^{-7}M$ ) and mepyramine maleate ( $10^{-6}M$ ), the latter to abolish the histamine response. (Brocklehurst, W.E. The release



of histamine and formation of a slow reacting substance (SRS-A) during anaphylactic shock. J. Physiol., Lond. 151, 416, 1960). Bulkied peritoneal fluids from passively sensitised and challenged rats were centrifuged, heated, stored at -20°C in 0.5 ml aliquots, and used as a reference SRS-A standard, and arbitrarily designated as containing 10 Units per ml. Concentrations of the unknown were bracketed by reference SRS-A samples. At the concentrations used, the compounds tested did not interfere with the assay.

### Results

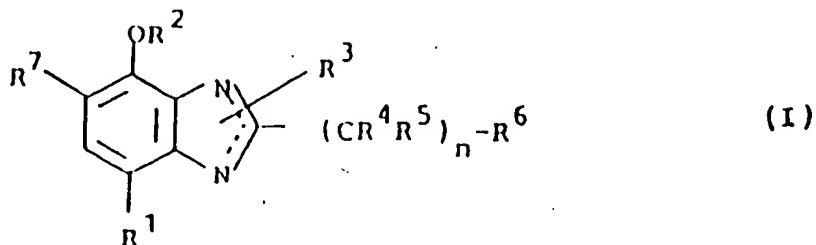
The results obtained in this test are shown in the following table and demonstrate the ability of the compounds of Examples 12, 25 and 26 to inhibit the release of SRS-A in this in vivo system. All compounds were given at a final concentration of  $2 \times 10^{-4}M$ .

Example No.	% inhibition of SRS-A release compared to controls.
12	58
25	59
26	55

No toxic effects were observed during any of these test procedures.

Claims

1. A compound of the general formula I



or a salt or solvate thereof, in which  $R^1$  represents hydrogen or a lower alkyl group,

$R^2$  represents hydrogen, a lower alkyl group, or  $\overset{\text{O}}{\parallel}\text{-CR}^8$ ,

$R^3$  represents hydrogen, a lower alkyl group, or  $\overset{\text{O}}{\parallel}\text{-CR}^8$ ,

$R^4$  represents hydrogen or a lower alkyl group,

$R^5$  represents hydrogen or a lower alkyl group,

$R^6$  represents hydrogen, a lower alkyl, a substituted or unsubstituted aryl group, or  $\text{-COOR}^{15}$ ,

$R^7$  represents hydrogen, halogen or lower alkyl,

$R^8$  represents a lower alkyl or a substituted or unsubstituted carbocyclic aryl group,

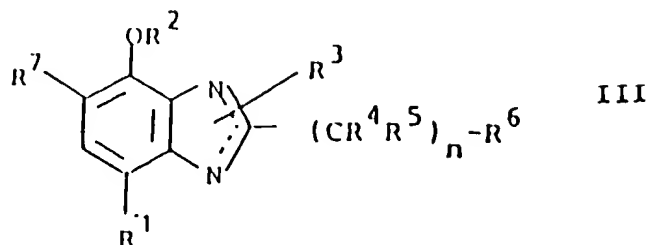
$R^{15}$  represents hydrogen or a lower alkyl,

and  $n$  is 0 to 8,  $n$  being 0 when  $R^6$  represents lower alkyl,

for use as an active therapeutic substance.

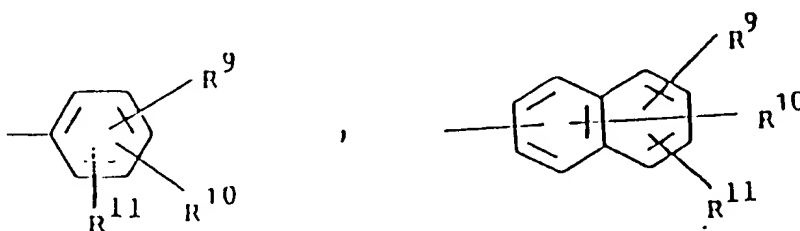
- 2 -

2. A compound of the general formula III



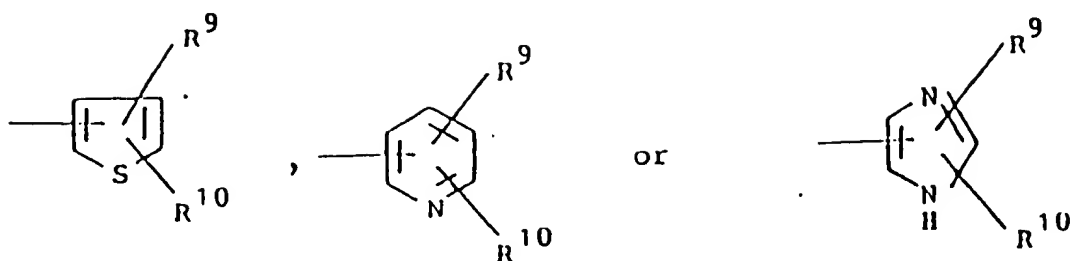
or a salt or solvate thereof, in which  $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$  and  $R^{15}$  are as defined for formula I, subject to the provisos that in a compound in which  $R^2$  and  $R^3$  represent hydrogen or lower alkyl,  $R^6$  represents hydrogen, lower alkyl or carbocyclic aryl,  $R^7$  represents H or alkyl and  $n = 0$ ,  $R^1$  does not represent hydrogen, and that in a compound in which  $R^1, R^2, R^6$  and  $R^7$  represent hydrogen or methyl and  $n = 0$ ,  $R^3$  does not represent hydrogen or an alkyl group having up to 4 carbon atoms.

3. A compound according to claim 1 or claim 2 in which  $R^6$  or  $R^8$  represents



or  $R^6$  represents

- 3 -



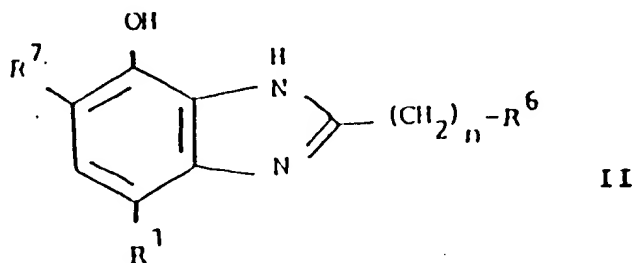
in which each  $R^9$ ,  $R^{10}$ ,  $R^{11}$  independently represents hydrogen, hydroxy, lower alkoxy, lower alkyl, halogen, trifluoromethyl, nitrile, nitro, amino,  $NR^{12}$   $R^{13}$  (in which  $R^{12}$  and  $R^{13}$  are independently hydrogen or lower alkyl),  $-COOH$ ,  $-COOR^{14}$ ,

$\begin{array}{c} O \\ || \\ -C-R^{14} \end{array}$ , or  $\begin{array}{c} O \\ || \\ -O-C-R^{14} \end{array}$  (in which  $R^{14}$  is lower alkyl or aryl), or in which  $R^9$  and  $R^{10}$  are linked and together represent methylenedioxy or  $C_3-C_4$  alkylene.

4. A compound according to any one of claims 1 to 3 in which  $R^2$  is a methyl group or  $COR^8$  in which  $R^8$  is a methyl group.

5. A compound according to any one of claims 1 to 4 in which  $R^4$  and  $R^5$  are hydrogen atoms.

6. A compound of general formula II:



II

or a salt or solvate thereof, in which  $R^1$  represents a lower alkyl group,  $R^7$  represents hydrogen or a lower alkyl group,  $R^6$  represents an aryl group, and  $n$  is 0 to 5.

01  
02 7. A compound according to any one of claims 1 to 6  
03 in which  $R^7$  is hydrogen or a tert.butyl group.  
04

05 8. A compound according to any one of claims 1 to 7  
06 in which  $R^6$  is a phenyl group mono-, di-, or  
07 tri-substituted by a methoxy or a methyl group.  
08

09 9. A compound according to claim 8 in which  $n = 1$ .  
10

11 10. A compound according to any one of claims 1 to 9  
12 in which  $R^1$  is a methyl group.  
13

14 11.  
15

16 2-benzyl-4-hydroxy-7-methylbenzimidazole;

17 2-(4-chlorobenzyl)-4-methoxy-7-methylbenzimidazole;

18 2-(4-chlorobenzyl)-4-hydroxy-7-methylbenzimidazole;

19 2-phenethyl-4-hydroxy-7-methylbenzimidazole

20 2-phenyl-4-hydroxy-7-methylbenzimidazole;

21 2-(pyrid-3-yl)methyl-4-hydroxy-7-methylbenzimidazole;

22 2-(naphth-2-ylmethyl)-4-hydroxy-7-methylbenzimidazole;

23 2-benzyl-4-hydroxy-5-tert-butyl-7-methylbenzimidazole;

24 5-tert-butyl-4-hydroxy-2-(4'-methoxybenzyl)-7-methyl-  
25 benzimidazole;

26 2-(4'-methylbenzyl)-4-hydroxy-7-methylbenzimidazole;

27 2-n-propyl-4-hydroxy-7-methylbenzimidazole;

28 2-(4'-methoxybenzyl)-4-hydroxy-7-methylbenzimidazole;

29 2-(3'-trifluoromethylbenzyl)-4-hydroxy-7-methylbenzimid-  
30 azole;

31 2-(4'-N,N-dimethylaminobenzyl)-4-hydroxy-7-methylbenzi-  
32 midazole;

33 2-naphth-1-ylmethyl)-4-hydroxy-7-methylbenzimidazole;

34 2-benzyl-4-hydroxybenzimidazole;

35 2-(4'-methoxybenzyl)-4-hydroxybenzimidazole;

36 6-(4-hydroxy-7-methyl-benzimidazole-2-yl)-hexanoic  
37 acid;

01 ethyl 6-(4-hydroxy-7-methyl-benzimidazole-2-yl)-  
02 hexanoate;  
03 ethyl 5-(4-hydroxy-7-methyl-benzimidazol-2yl)-  
04 pentanoate;  
05 5-(4-hydroxy-7-methyl-benzimidazol-2yl)-pentanoic acid;  
06 2-(2'-furyl)-4-hydroxy-7-methylbenzimidazole;  
07 2-(thien-2-ylmethyl)-4-hydroxy-7-methylbenzimidazole;  
08 2-(4'-ethoxybenzyl)-4-hydroxy-7-methylbenzimidazole;  
09 2-(3',4',5'-trimethoxybenzyl)-4-hydroxy-7-methylbenzi-  
10 midazole;  
11 2-(3',4'-dimethoxybenzyl)-4-hydroxy-7-methylbenzimidaza-  
12 zole;  
13 2-(3'-methoxybenzyl)-4-hydroxy-7-methylbenzimidazole;  
14 2-(4'-methoxyphenyl)-4-hydroxy-7-methylbenzimidazole;  
15 2-(2'-methoxybenzyl)-4-hydroxy-7-methylbenzimidazole;  
16 or  
17 2-(4'-hydroxybenzyl)-4-hydroxy-7-methylbenzimidazole.  
18  
19

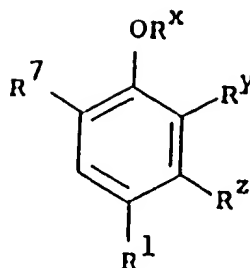
12.

21  
22 2-(1-phenylethyl)-4-hydroxy-7-methylbenzimidazole;  
23 2-(thien-2-yl)-4-hydroxy-7-methylbenzimidazole;  
24 2-(imidazol-1-yl)methyl-4-hydroxy-7-methylbenzimidazole  
25 2-benzyl-3-acetyl-4-hydroxy-7-methylbenzimidazole;  
26 1-acetyl-2-benzyl-4-hydroxy-7-methylbenzimidazole;  
27 2-benzyl-4-hydroxy-5-chloro-7-methylbenzimidazole;  
28 2-n-hexyl-4-hydroxy-5-tert.-butyl-7-methylbenzimidazole  
29 2-benzyl-4-hydroxy-5-tert.-butyl-benzimidazole;  
30 2-benzyl-3-acetyl-4-hydroxy-5-chloro-benzimidazole; or  
31 1-acetyl-2-benzyl-4-hydroxy-5-chloro-benzimidazole.  
32

33 13. A pharmaceutical composition comprising a  
34 physiologically tolerable compound as claimed in claim  
35 1 together with a physiologically tolerable carrier.  
36

- 6 -

14. A compound of the formula IX:



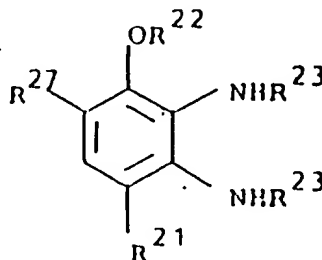
(IX)

in which  $R^1$  is as defined for formula I,  $R^X$  is benzyl or mesyl or  $R^2$  as defined for formula I,  $R^Y$  is hydrogen,  $NO_2$  or  $NH_2$ ,  $R^Z$  is  $NO_2$  or  $NH_2$ ,  $R^7$  is tert. butyl.

15.

2-nitro-4-hydroxy-5-tert-butyltoluene-O-mesylate;  
2-nitro-4-hydroxy-5-tert-butyltoluene;  
2,3-dinitro-4-hydroxy-5-tert-butyltoluene; or  
2,3-diamino-4-hydroxy-5-tert-butyltoluene.

16. A process for the manufacture of a compound according to claim 1 or 2, wherein a compound of the formula IV



(IV)

wherein  $R^{21}$  represents hydrogen or a lower alkyl group, or a group or atom convertible thereto,  $R^{22}$  represents hydrogen or a lower alkyl group, or a group or atom

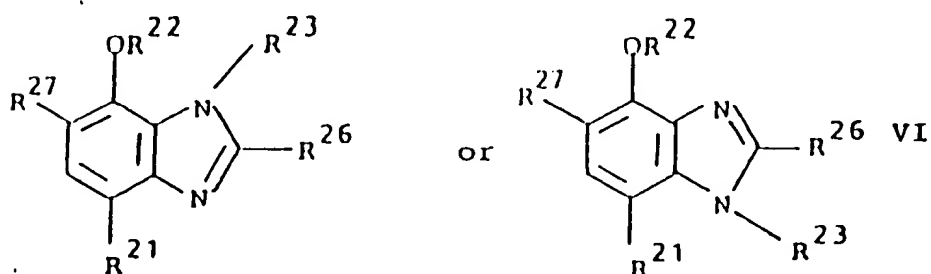
- 7 -

convertible thereto, on  $R^{23}$  represents hydrogen and the other  $R^{23}$  represents hydrogen or a lower alkyl group, or a group or atom convertible thereto, and wherein  $R^{27}$  represents hydrogen, halogen, or alkyl, or a group or atom convertible thereto, is reacted with a compound of formula V



V

wherein  $R^{26}$  represents  $-(CR^4R^5)_n-R^6$ , or a group convertible thereto, wherein  $R^4$ ,  $R^5$ , and  $R^6$ , and  $n$  each have the meanings defined in claims 1 and 2 with reference to formula I or formula III and  $R^{28}$  represents a leaving group or hydrogen to form a compound of the formula VI:



and, if required, a nitrogen atom of, and/or the 4-oxygen atom on, the benzimidazole nucleus is acylated

with a group of the formula  $\overset{O}{\parallel} CR^8$  or is alkylated, and if required protecting groups are removed, and if required a salt or solvate is formed.



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17. A benzimidazole having an optionally etherified or esterified hydroxy group in the 4-position and a lipophilic group, for use as an active therapeutic substance.

18. A compound according to claim 17 in which the lipophilic group is in the 2-position.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0178413

EP 85 11 0076

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	US-A-3 856 810 (KALOPISSIS)		C 07 D 235/18 C 07 D 235/16 C 07 D 235/14 C 07 D 235/10 C 07 D 235/08
A	GB-A-1 274 786 (CIBA)		C 07 D 401/06 C 07 D 405/04 C 07 D 409/06 C 07 D 409/04 C 07 D 403/06 A 61 K 31/415
A	EP-A-O 000 784 (BOEHRINGER)		
A	DE-A-2 628 716 (OREAL)		
A	JOURNAL OF THE CHEMICAL SOCIETY, Perkin Transactions I, 1972, pages 396-408; R.K. HAYNES et al.: "Amine oxidation and the chemistry of quinone imines. Part I. 3-methoxy-4-t-butylaniline"		TECHNICAL FIELDS SEARCHED (Int. Cl. 4)  C 07 D 235/00 C 07 D 401/00 C 07 D 405/00 C 07 D 409/00 C 07 D 403/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 16-12-1985	Examiner DE BUYSER I.A.F.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document but published on, or after the filing date D : document cited in the application L : document cited for other reasons  A : member of the same patent family, corresponding document	